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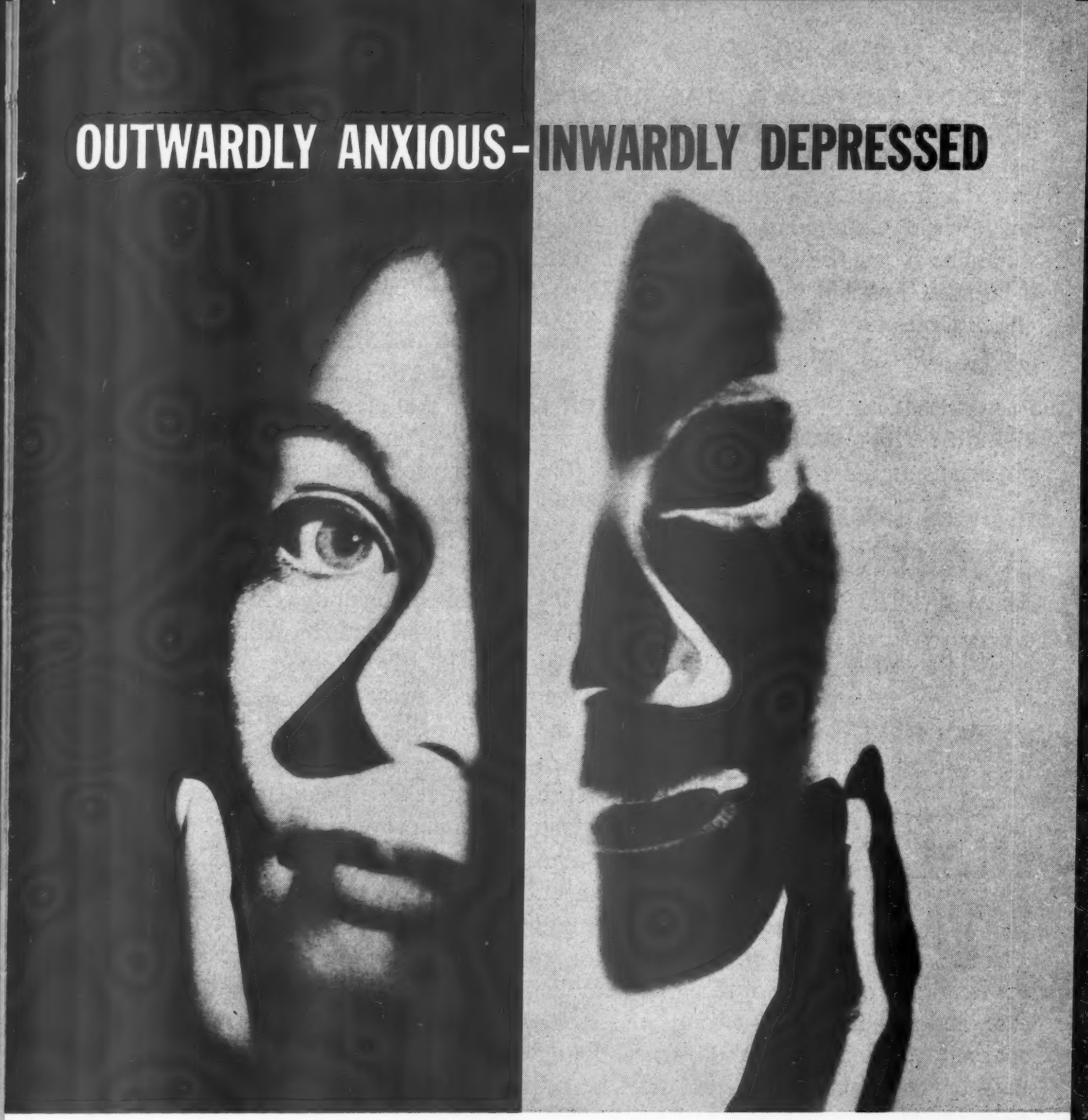
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Hereditary Nephropathy, Deafness and Renal Foam Cells
ROBERT E. WHALEN, SHAONAN HUANG, ERNST PESCHEL AND HENRY D. MCINTOSH 171

This study treats of several interesting topics: hereditary nephropathy and the nature of the structural abnormalities of the kidney responsible for it; the association with deafness, of which the family herein described is the thirteenth recorded in detail; and the significance of renal foam cells, hitherto regarded by some as pathognomonic of hereditary nephropathy, a view disproved by the authors. The whole constitutes yet another genetically transmitted disorder. Speculations as to possible pathogenesis are reviewed.

Familial Growth Retardation, Renal Aminoaciduria and Cor Pulmonale. I. Description of a New Syndrome, with Case Reports
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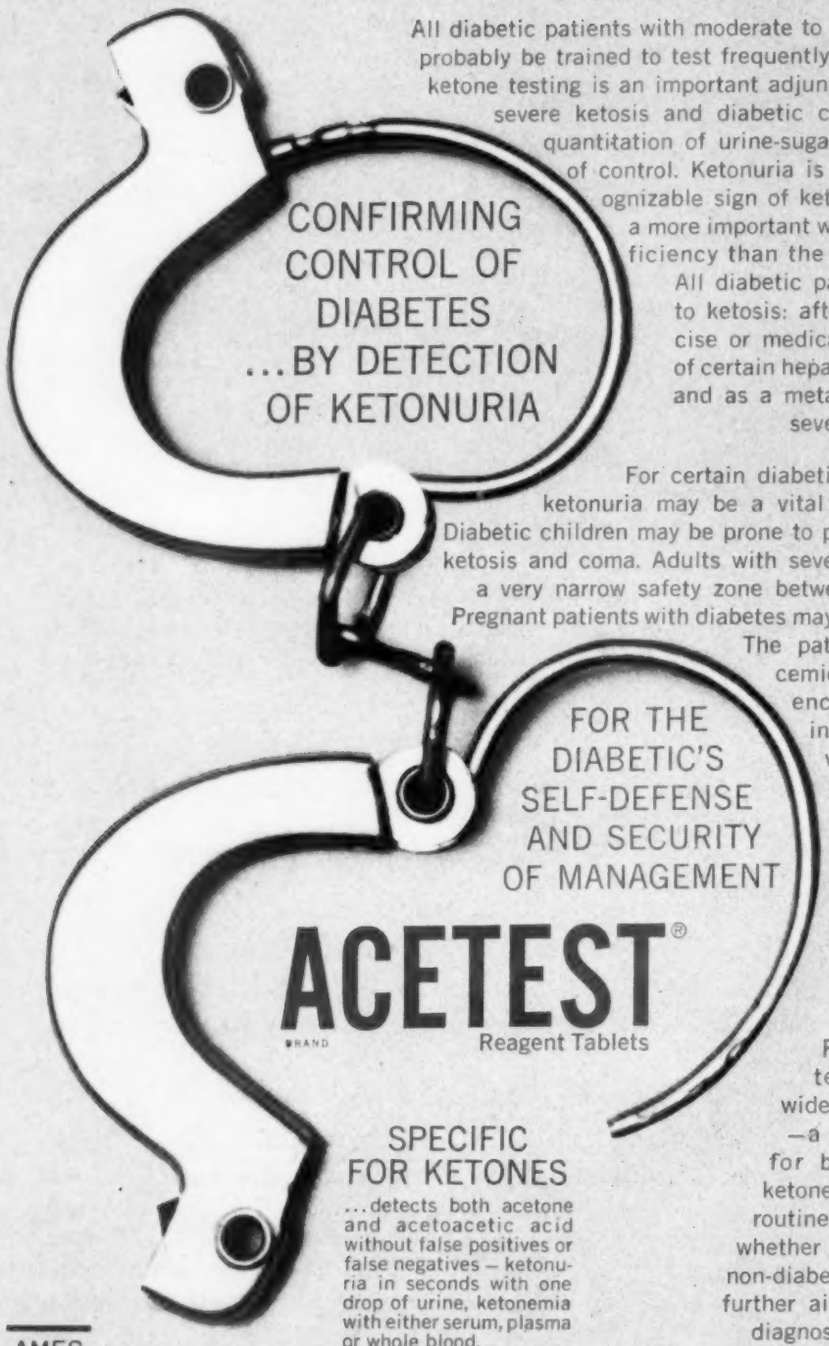
A New Syndrome: Familial Growth Retardation, Renal Aminoaciduria and Cor Pulmonale. II. Investigation of Renal Function, Amino Acid Metabolism and Genetic Transmission
LEON E. ROSENBERG, PETER S. MUELLER AND DONALD M. WATKIN 205

The first paper outlines the clinical and general laboratory findings in three of six sibling children who presented a syndrome characterized clinically by growth retardation, poor muscular development, scanty adipose tissue and pulmonary and cardiac abnormalities, all apt to lead to early death. The most striking laboratory finding was a renal tubular defect resulting in isolated aminoaciduria. The second paper enlarges upon the abnormality in tubular reabsorption of amino acids, notably of serine, threonine, lysine, histidine and tyrosine, less conspicuously of alanine, glycine and phenylalanine. The possibility that the failure to thrive might be due to loss of "essential" and other amino acids was explored by replacement therapy, but without striking results.

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CONFIRMING CONTROL OF DIABETES ...BY DETECTION OF KETONURIA

All diabetic patients with moderate to severe diabetes should probably be trained to test frequently for ketonuria. Routine ketone testing is an important adjunct in the prevention of severe ketosis and diabetic coma, just as frequent quantitation of urine-sugar indicates the degree of control. Ketonuria is not only the first recognizable sign of ketosis,[1] but also may be a more important warning of insulin-insufficiency than the degree of glucosuria. All diabetic patients can be subject to ketosis: after errors of diet, exercise or medication; in the presence of certain hepatic and renal disorders; and as a metabolic consequence of severe infection or stress.

For certain diabetic patients, testing for ketonuria may be a vital part of daily routine. Diabetic children may be prone to precipitous episodes of ketosis and coma. Adults with severe diabetes may have a very narrow safety zone between control and coma. Pregnant patients with diabetes may easily become ketotic. The patient on oral hypoglycemic therapy may experience drug failure, need insulin temporarily or develop unwise habits of diet or medication—ample justification for his self-defense with routine testing for ketonuria.

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(1) Duncan, G. G.: Diseases of Metabolism, ed. 4, Philadelphia, Saunders, 1959, p. 795.
(2) Lee C. T., and Duncan G. G.: Metabolism 5:144, 1956.

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Diabetic Glomerulosclerosis. A Long-Term Follow-Up Study Based on Renal Biopsies
F. E. HATCH, M. F. WATT, N. C. KRAMER, A. E. PARRISH AND J. S. HOWE 216

The authors describe their findings in a sizeable group of patients with diabetes and evidence of concomitant renal disease who were studied by needle biopsy of the kidney (in some instances serially) as well as by the more conventional parameters. Examination of the biopsy material was limited to light microscopy. Like other investigators, diffuse and mixed (combined nodular and diffuse) lesions of diabetic glomerulosclerosis were observed, each type signifying a somewhat different course. The data are carefully analyzed to reveal what manifestations can be considered to imply the presence of either form of diabetic glomerulosclerosis and various hints are proposed although conclusive criteria could not be extracted. The general implications are discussed informatively.

Comparative Study of Serum Leucine Aminopeptidase, 5-Nucleotidase and Nonspecific Alkaline Phosphatase in Diseases Affecting the Pancreas, Hepatobiliary Tree and Bone
O. DHODANAND KOWLESSAR, LORRAINE J. HAEFFNER, ERLA M. RILEY AND MARVIN H. SLEISENGER 231

The present survey of serum leucine aminopeptidase activity (LAP) in a large group of normal subjects and patients with disease of the pancreas, hepatobiliary system or bone clarifies the relationship of this enzyme to disorders of the organs studied. Elevated values were obtained in pancreatic disease only when the hepatobiliary system was affected, and in obstructive disease of the latter when the pancreas was unaffected. The inference is obvious that, like serum alkaline phosphatase and 5-nucleotidase (5N), the serum LAP reflects alterations in the patency of the extra- or intrahepatic biliary tract; concurrent determinations of all three enzymes demonstrate this. It is also shown that LAP and 5N help to distinguish whether or not increased serum alkaline phosphatase levels are due to primary hepatobiliary or skeletal disease.

Manifestations of Metastatic Tumors of the Liver. A Study of Eighty-One Patients Subjected to Needle Biopsy L. FREDERICK FENSTER AND GERALD KLATSKIN 238

This paper deals with one of the oldest problems in medicine, yet one that is always with us and, as the authors point out, rarely considered in sufficient detail and not as thoroughly as herein. The result is an informative analysis which stresses manifestations of hepatic metastases that are often the cause of diagnostic uncertainty and confusion; pain in the region of the liver, fever, portal hypertension, ascites, a friction rub over the liver, all associated with little or no jaundice. Laboratorywise, delayed bromsulphalein excretion and increased serum alkaline phosphatase were most consistently found, doubtless reflecting obstruction of the intrahepatic biliary tract. Needle biopsy of the liver, although it samples only approximately one fifty-thousandth of the liver mass, yielded carcinoma in 78 per cent of the eighty-one patients studied, to be sure most of them with advanced involvement of the liver; the risk was negligible.

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Chronic Chlorpromazine Jaundice. With Particular Reference to Its Relationship to Primary Biliary Cirrhosis

A. E. READ, C. V. HARRISON AND SHEILA SHERLOCK 249

Four well documented cases of this interesting and still quite obscure form of drug reaction are described. Particularly valuable are the notes on the progressive changes observed in serial biopsies of the liver and in the chemical abnormalities of the blood. Despite the many similarities of this syndrome to primary biliary cirrhosis, there are significant differences which make possible the differentiation, important particularly because of the fatal course of primary biliary cirrhosis.

Aspirin and Gastrointestinal Bleeding. Chromate^{51} Blood Loss Studies

RICHARD N. PIERSON, JR., PETER R. HOLT, RICHARD M. WATSON AND RICHARD P. KEATING 259

In this study, blood loss following ingestion of salicylates was measured by tagging red cells with chromate^{51} and measuring the radioactivity of the stools (presumed to derive from gastrointestinal bleeding) in 148 subjects free of overt disease of the stomach or intestines. With aspirin, whether taken as intact tablets, powder or enteric-coated, blood loss more or less in excess of that in premedication control periods was noted in about three-fourths of the subjects. Total dosage and frequency of administration were factors related to the quantity of blood lost. Salicylate preparations very soluble in water caused little or no gastrointestinal bleeding.

Aspirin and Gastric Bleeding. Gastroscopic Observations, with Review of Literature

ALEX WEISS, ERNEST R. PITMAN AND EMERSON C. GRAHAM 266

This much discussed subject is here considered in the light of direct gastroscopic observation before and immediately after the administration of salicylates. The results leave no doubt that in some persons, notably those with pre-existing abnormalities of the gastric mucosa, salicylate induces congestive and hemorrhagic changes by a direct irritant action on the mucosa.

Review

Chronic Pulmonary Emphysema. Anatomy and Pathogenesis

A. G. HEPPLESTON AND J. C. LEOPOLD 279

This representation of the views of the "Cardiff School" on the nature and pathogenesis of emphysema is a carefully thought out interpretation of many years of study of the microanatomy of emphysema, as it occurs particularly in a coal mining center. The authors propose a classification according to the airways mainly affected: focal emphysema due to dust and centrilobular emphysema when the respiratory bronchioles are chiefly involved, "vesicular" emphysema when the alveolar ducts and alveolar sacs are the focal point of abnormality, and an irregular form designated scar emphysema. Each category is described in detail and differentiated from the others. Of particular interest is the conclusion from the anatomic evidence that physiologic obstruction to air flow is a result, not a primary cause, of pulmonary emphysema.

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The Association of Polycythemia with a Cerebellar Hemangioblastoma. The Production of an Erythropoiesis Stimulating Factor by the Tumor

THOMAS A. WALDMANN, EDGAR H. LEVIN AND MAITLAND BALDWIN 318

This study explains the puzzling association of von Hippel-Lindau syndrome (cerebellar hemangioblastoma) with polycythemia by demonstrating the presence of a substance possessing erythropoiesis-stimulating properties (an erythropoietive) in the tumor.

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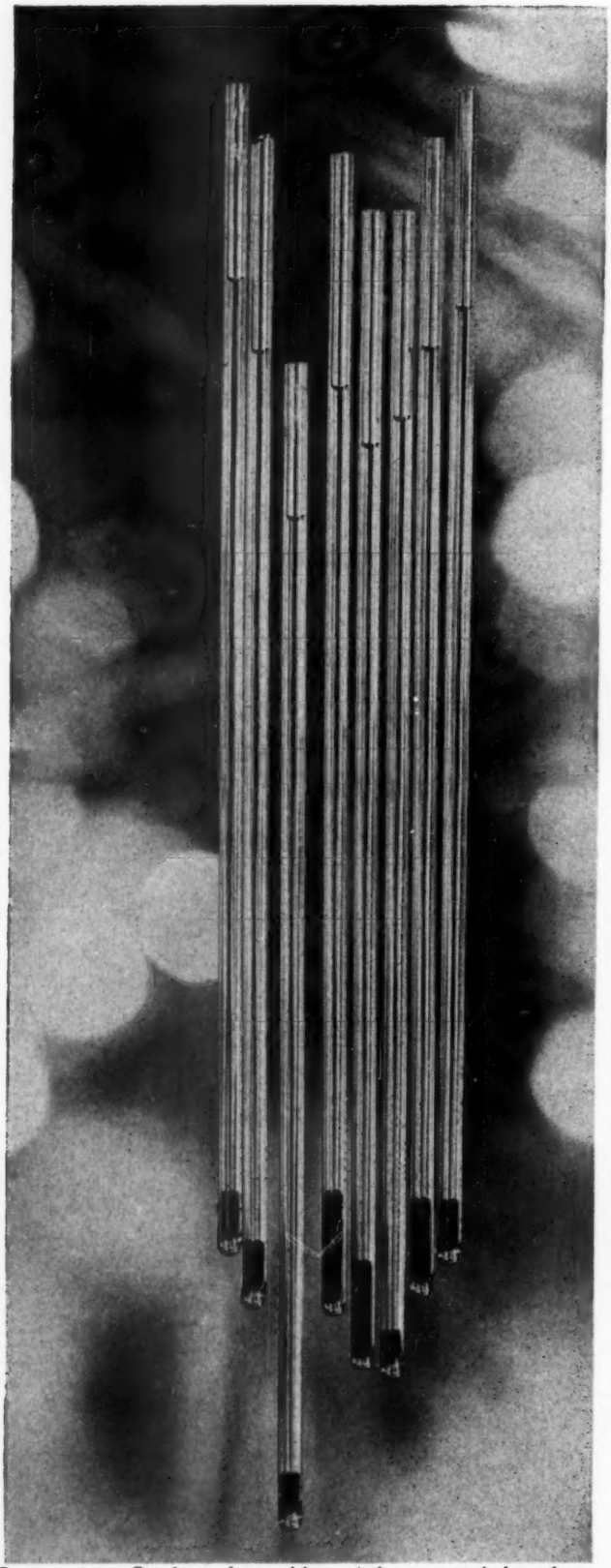
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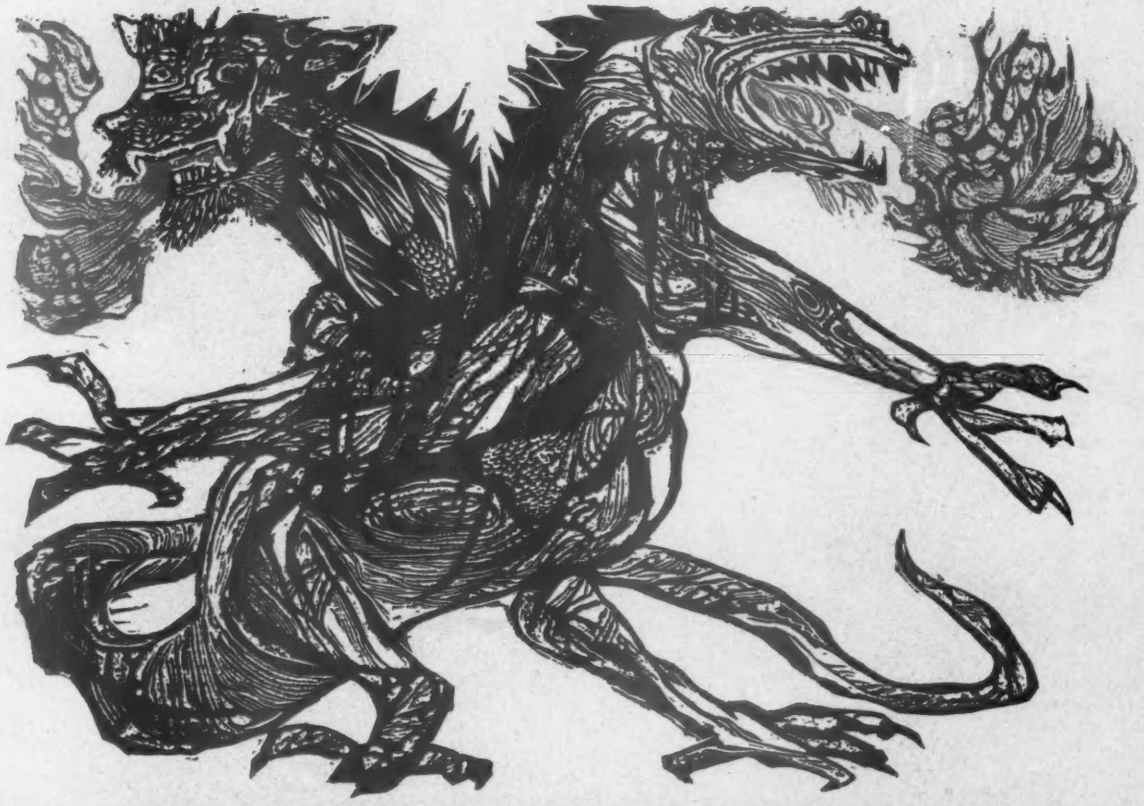
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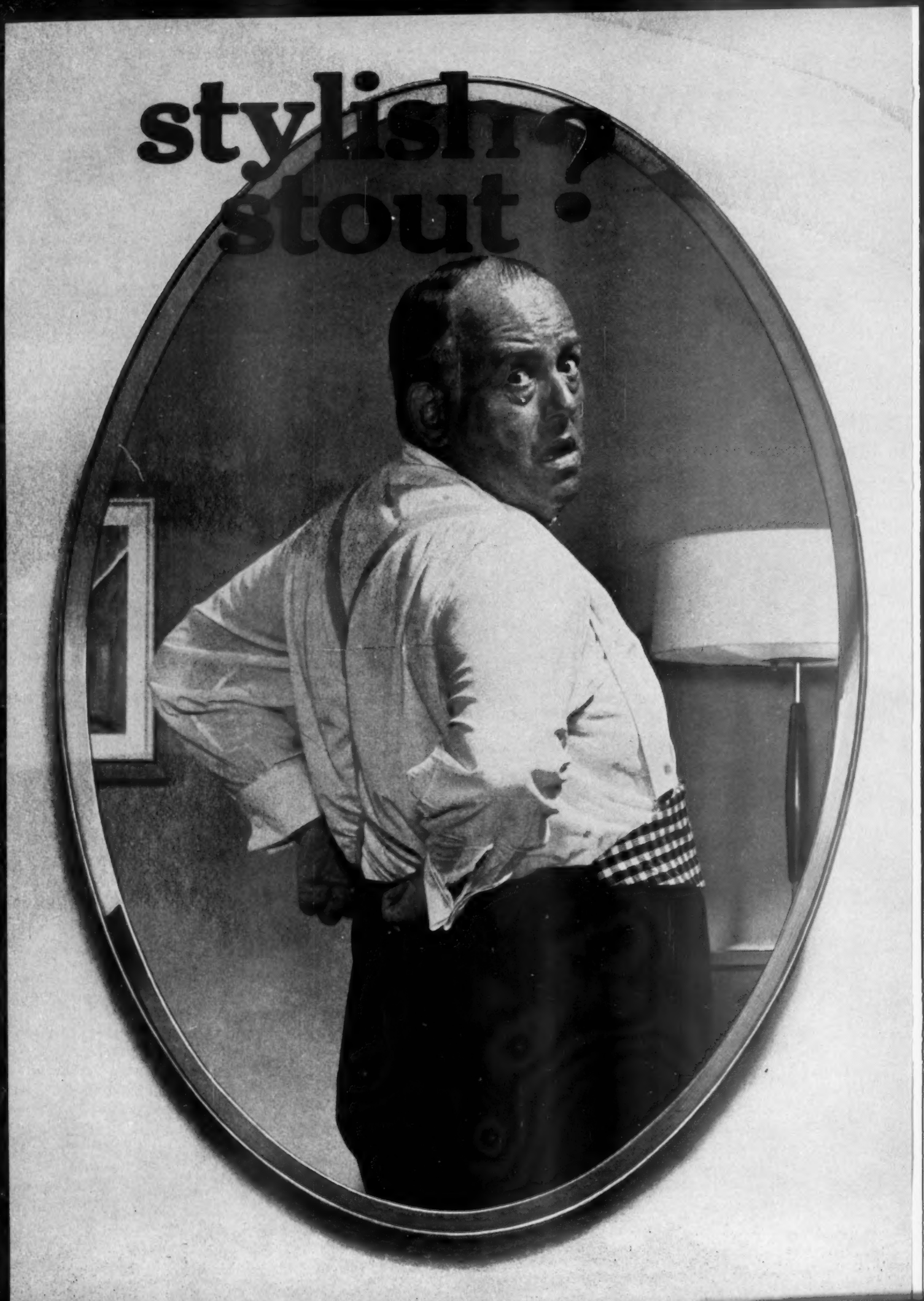
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Rapid and complete absorption, without the uncertainty of oral or buccal enzyme therapy.[5]

more potent than salicylates—
Anti-inflammatory potency of Tandearil markedly superior to aspirin.[12]

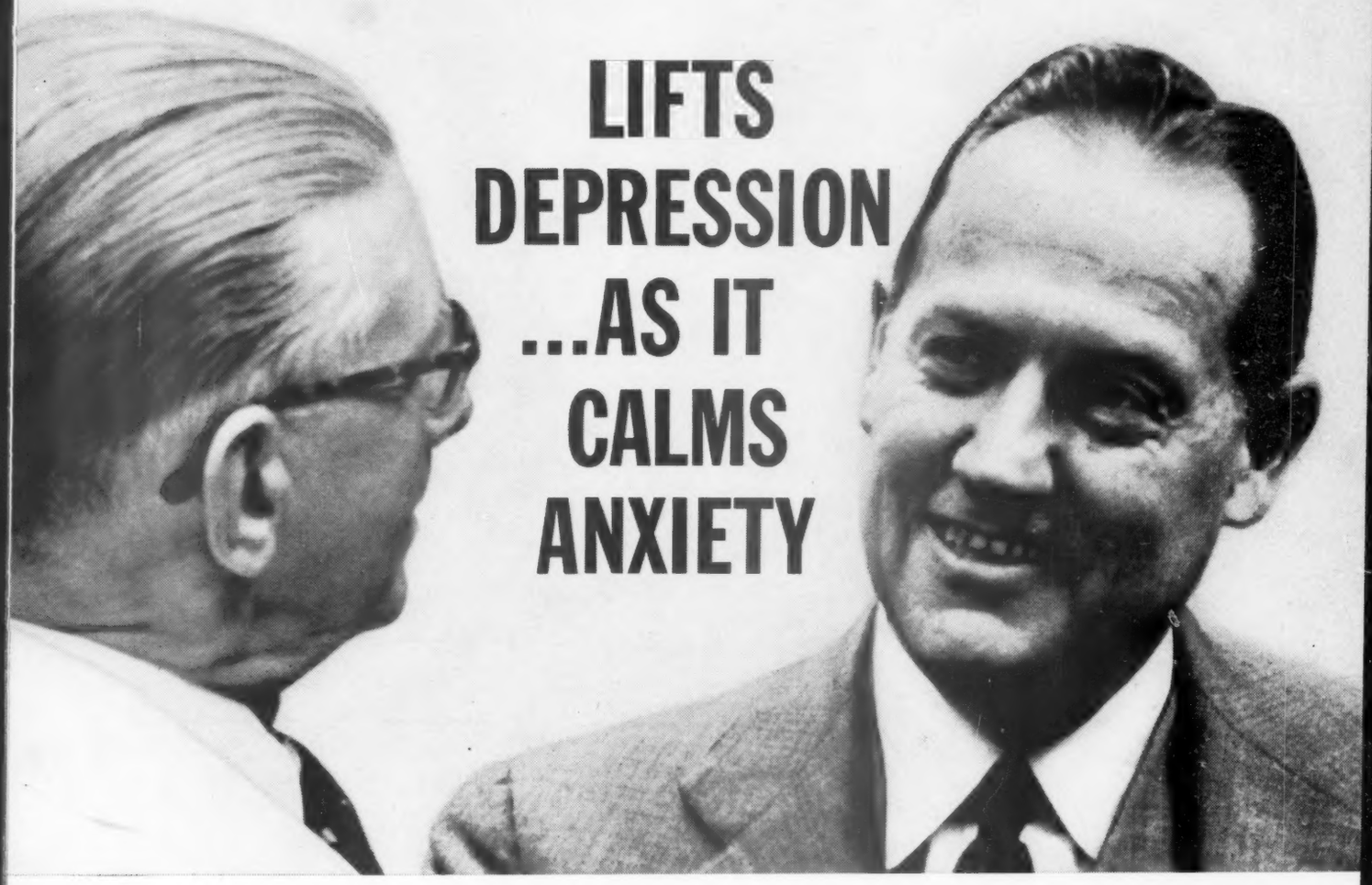
Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1,2,3]; gout[1,4,5]; acute superficial thrombophlebitis[6,7]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1,4]; severe forms of a variety of local inflammatory conditions[8,9,10].

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing. Full product information available on request.

availability:
Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

references:
1. Graham, W.: Canad. M.A.J.: 82:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Klem, I. M.: Arth. and Rheumat. 2:212, 1959. 3. O'Reilly, T. J.: J. Irish M.A. 46:106, 1960. 4. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. 98:31, 1959. 5. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 6. Stein, I. D.: Ann. N. Y. Acad. Sc. 86:307 (March 30) 1960. 7. Barczyk, W., and Röth, W.: Praxis 49:589, 1960. 8. Miller, J. M., et al.: Antibiotic Med. and Clin. Therapy, 7:102, 1960. 9. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. 97:429, 1959. 10. Summary of individual case histories submitted to Geigy. 11. Domenjoz, R.: Ann. N. Y. Acad. Sc. 86:263, 1960. 12. Smyth, C. J.: Ann. N. Y. Acad. Sc. 86:292, 1960.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York
545-61



LIFTS DEPRESSION ...AS IT CALMS ANXIETY

Thanks to your balanced Deprol therapy... his depression has lifted and his mood has brightened up – while his anxiety and tension have been calmed down. He sleeps better, eats properly, and normal drive and interest have replaced his emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly – you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver toxicity, hypotension or tachycardia.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

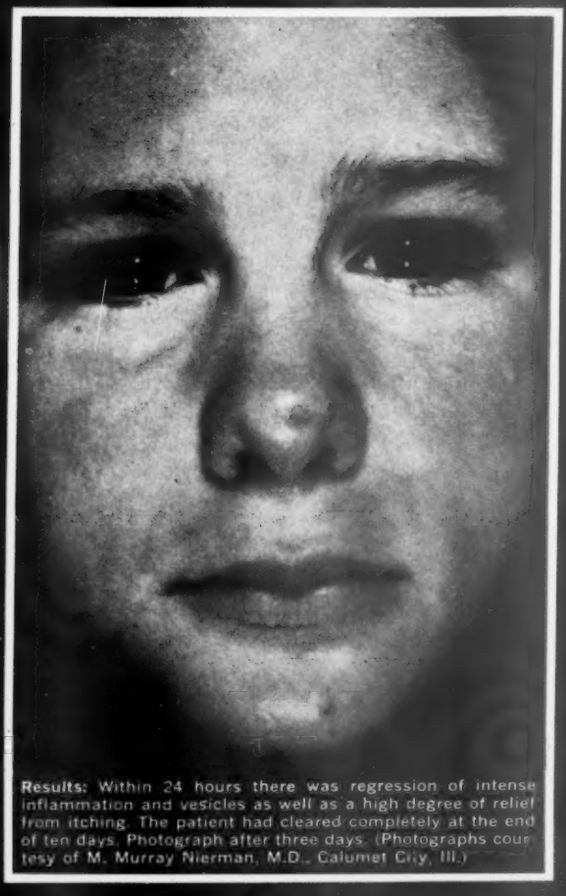
WALLACE LABORATORIES / *Cranbury, N. J.*

CD-4489



Male, Age 9; Dx: Poison Ivy Dermatitis.
Rx: Celestone, 1 tab. q.i.d. for two days, 1 tab. t.i.d. for two days, 1 tab. b.i.d. for one week, and 1 tab. daily for 7 days. Photograph shows the patient before treatment.

Allergic/inflammatory flare-up!



Results: Within 24 hours there was regression of intense inflammation and vesicles as well as a high degree of relief from itching. The patient had cleared completely at the end of ten days. Photograph after three days. (Photographs courtesy of M. Murray Nierman, M.D., Calumet City, Ill.)

Schering

A new achievement in corticosteroid activity: CELESTONE (betamethasone) has been called "perhaps the most important step ahead since the discovery of prednisone and prednisolone..."[1] and "unquestionably the most active adrenocortical steroid we have studied to date."[2] Pre-introductory clinical studies have established not only the high antiallergic/anti-inflammatory activity of CELESTONE but also its "low incidence of side effects...[and] absence of new toxic effects...."[3]

Three significant clinical advantages: In reporting results of a study of 154 dermatologic patients, treated up to 9 months, the investigators[1] cite as "three important clinical advantages of betamethasone [CELESTONE]: its almost uniform effectiveness at exceptionally low dosages, the striking absence of hormonal side effects in our series, and the ability of this corticosteroid to elicit a good therapeutic response in patients who had previously done poorly on other steroids."

Rapid remission with new Celestone

the first major advance in corticosteroid therapy in over 2½ years

Greater utility–ease of use: Gratifying results have been achieved with CELESTONE in a broad range of steroid-responsive disorders, from bronchial asthma and pollenosis to allergic dermatoses, inflammatory ocular diseases and rheumatoid arthritis. Rapid subsidence of allergic or inflammatory flare-up can usually be expected on average daily dosages of from 2 to 8 tablets. The single tablet strength (0.6 mg.) simplifies dosage schedules and facilitates proper dosage adjustment when patients are switched from other corticosteroids.

H-399

Safety-speed factor: Results with CELESTONE in 353 dermatologic patients[2] indicate that "its high degree of effectiveness and virtual absence of side effects in low dosages, which permit a simplified therapeutic regimen, make betamethasone [CELESTONE] an exceptionally useful corticosteroid in acute, short-term conditions."

For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

Bibliography: 1. Gant, J.Q., and Gould, A.H.: Betamethasone: A Clinical Study. Paper presented at First Conference on the Clinical Application of Betamethasone – A New Corticosteroid, New York City, May 8, 1961. 2. Nierman, M.M.: The Use of Betamethasone in Dermatology. *Ibid.* 3. Frank, L.: The Place of Betamethasone in Dermatologic Practice. *Ibid.*

NEW CELESTONE™

(betamethasone) **Tablets 0.6 mg.**



Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® succinylsulfathiazole—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help provide rapid symptomatic relief.

Additional information on **CREMOMYCIN** is available to physicians on request.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

CREMOMYCIN AND SULFASUXIDINE ARE TRADEMARKS OF MERCK & CO., INC.

Hypertension of 7 years' duration yields to Ser-Ap-Es®

Photo used with patient's permission.



Combination brings blood pressure down after other agents fail—During the past 7 years, Mrs. E. A.'s hypertension gradually advanced in severity. In 1956 and 1957 multiple retinal hemorrhages occurred in the right eye, and vision in this eye deteriorated. Retinopathy advanced to Grade III; EKG showed left ventricular hypertrophy; renal studies showed increasing involvement.

A wide variety of antihypertensive agents (including ganglionic blockers) failed to stabilize blood pressure at satisfactory levels or caused troublesome side effects.

When therapy with Ser-Ap-Es was started, Mrs. A.'s blood pressure (sitting and standing) was 230/120 mm. Hg. With Ser-Ap-Es, blood pressure (sitting and standing) has now been reduced to 190/90, and Mrs. E. A. enjoys a measure of control that had not been achieved with previous agents.

Because it provides 4 actions—central, cardiac, renal, and vascular—in one convenient tablet, Ser-Ap-Es can help you bring more of your hypertensive patients under control.

SUPPLIED: *Tablets* (salmon pink), each containing 0.1 mg. Serpasil, 25 mg. Apresoline hydrochloride, and 15 mg. Esidrix.

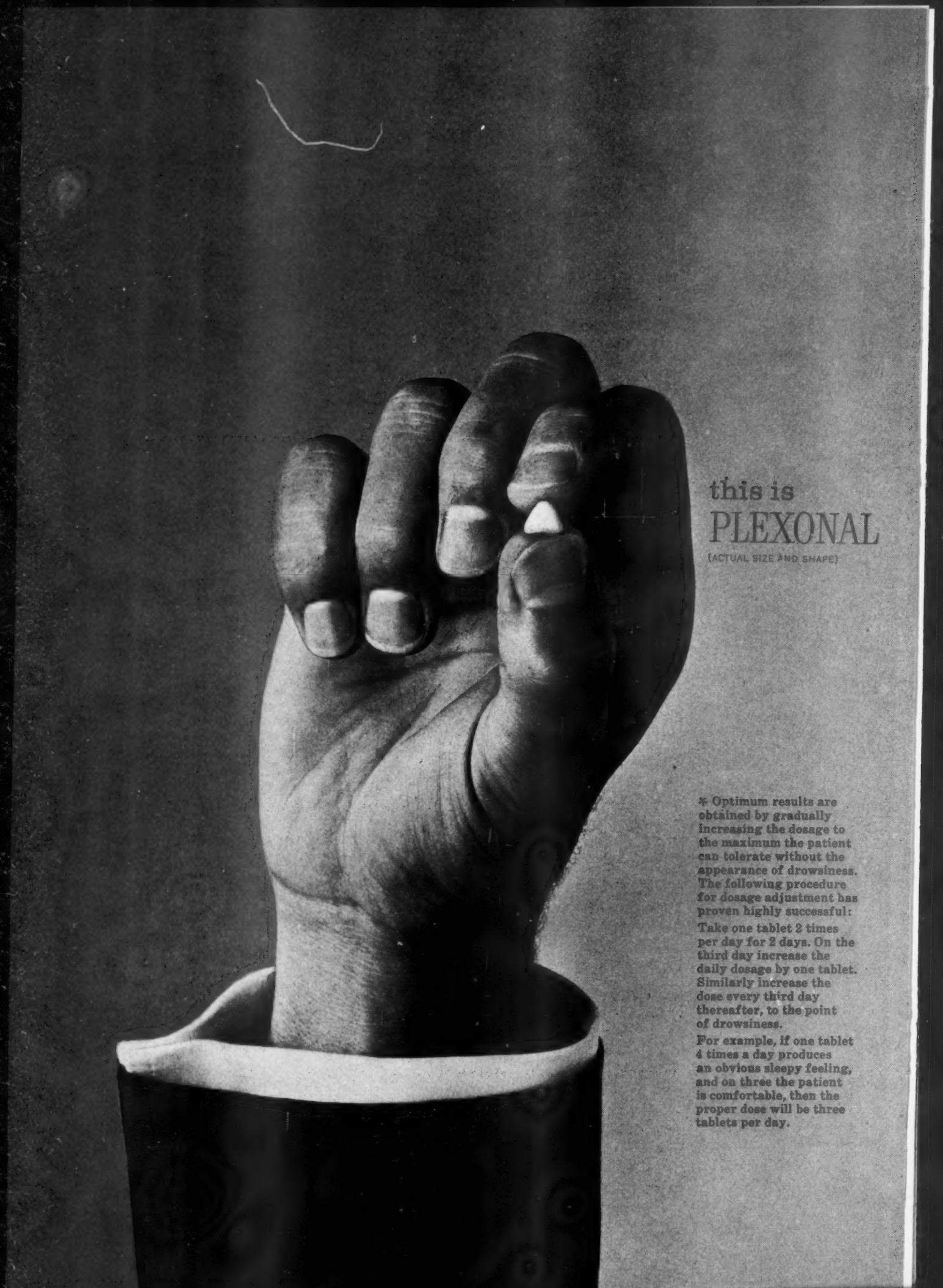
For complete information about Ser-Ap-Es (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N. J. 2/2923MK

SERPASIL® (reserpine CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
ESIDRIX® (hydrochlorothiazide CIBA)

The actions of Serpasil®, Apresoline® and Esidrix® in a single tablet:

Ser-Ap-Es

CIBA SUMMIT, NEW JERSEY



* Optimum results are obtained by gradually increasing the dosage to the maximum the patient can tolerate without the appearance of drowsiness. The following procedure for dosage adjustment has proven highly successful:

Take one tablet 2 times per day for 2 days. On the third day increase the daily dosage by one tablet. Similarly increase the dose every third day thereafter, to the point of drowsiness.

For example, if one tablet 4 times a day produces an obvious sleepy feeling, and on three the patient is comfortable, then the proper dose will be three tablets per day.

a superior daytime relaxing agent

(NOT A TRANQUILIZER)

PLEXONAL®

Comparative clinical studies show that PLEXONAL is superior to meprobamate or barbiturates for daytime relaxation[1,2]

"Plexonal was preferred (superior therapeutic effect) by 73.7 per cent of the patients, whereas 11.1 per cent preferred meprobamate, a ratio of 6.6 to 1. . . . 30.5 per cent noted adverse reactions to meprobamate as compared to 7 per cent in respect to Plexonal. . . . Plexonal gave better results than did any of the sedative or relaxing agents that have been available during our experience covering the previous 15 years."[1]

In 26 older age cardiac patients, "A comparison of Plexonal with the therapy previously employed showed that 17 did better on Plexonal than on meprobamate, 6 did better on meprobamate than on Plexonal and 3 responded the same to both."[2]

Indications: Anxiety, tension, apprehension, nervousness, irritability, restlessness, hyperexcitability.

Extremely well tolerated by geriatric patients who need mild sedation, as well as by depressed patients.

Dosage: One tablet 3 or 4 times a day is adequate for most patients. However, some require up to six tablets per day, whereas others respond adequately to as little as 1 tablet per day.*

Composition: Each tablet contains sodium diethylbarbiturate 45 mg., sodium phenylethylbarbiturate 15 mg., sodium isobutylallylbarbiturate 25 mg., scopolamine hydrobromide 0.08 mg., dihydroergotamine methanesulfonate 0.16 mg.

1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.

ORIGINAL RESEARCH SERVING THE PHYSICIAN

SANDOZ

Hostile Environment...



The fungus, protozoa and bacteria that commonly cause mild and severe leukorrhea require a vaginal pH of 5 to 12 for proliferation.

Trimagill creates a hostile environment! It produces a pH of 2.0 to 2.5—*the three principal infecting organisms cannot live in this acid range.*

Trimagill is well tolerated and has been proved effective in thousands of cases of leukorrhea, vaginitis, cervicitis, moniliasis and mixed infections. No untoward reactions that would require discontinuation of treatment were reported. At times denuded mucous membranes are so irritated that Trimagill may give a *temporary* burning sensation. This is usually short lived.

Trimagill does not foster resistant mutants or result in monilia overgrowth. Trimagill may be used during menstruation.

CONTENTS: Tartaric Acid, Citric Acid, Boric Acid, Dextrose, Potassium Alum, Potassium Bitartrate and Adhesives.

SUPPLIED: Powder: 5-oz. Plastic Insufflator Bottles; Vaginal Inserts: Boxes of 24.

NOTE: Consult package circular for information on dosage and instructions for use.

Write for descriptive literature.

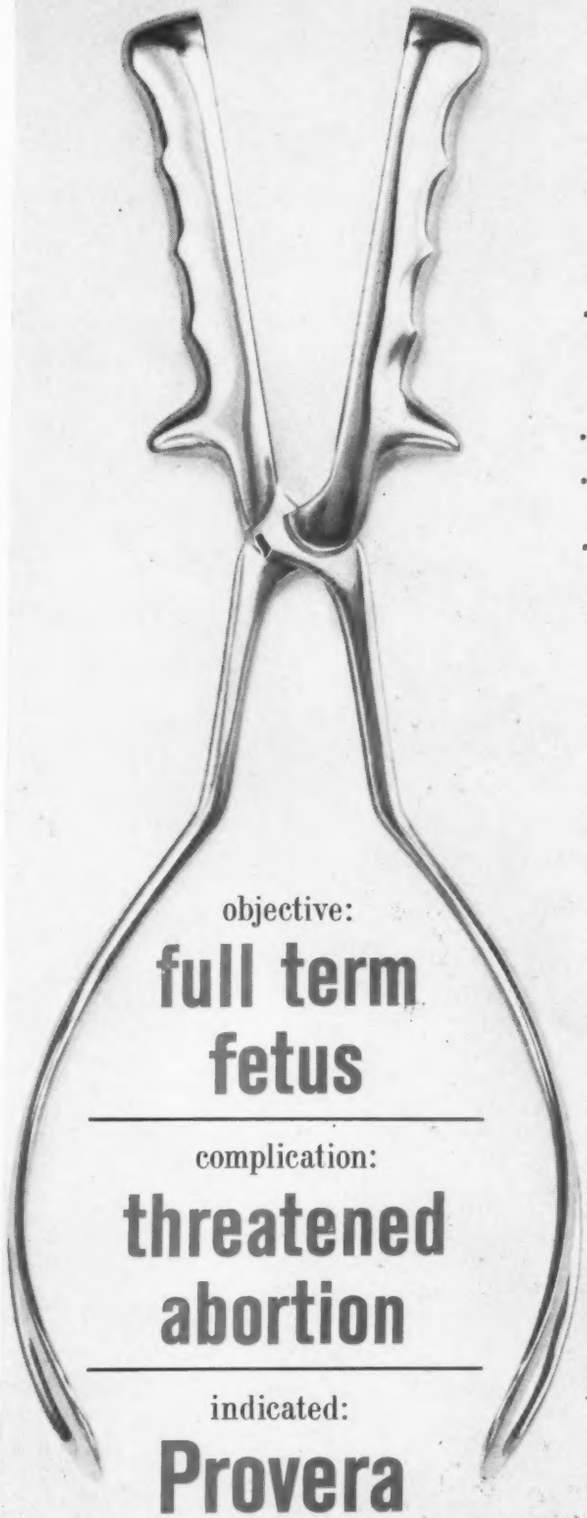
TRIMAGILL®*

POWDER • VAGINAL INSERTS

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

*Patent applied for.



objective:

full term fetus

complication:

threatened abortion

indicated:

Provera

Upjohn

Here are four reasons why:

- Provera is the only commercially – available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized animals.
- No significant side effects have been encountered.
- It is available for both oral and parenteral administration.
- Provera gives the economy of effective action from small doses.

Brief Basic Information

	◐ Oral Provera*	I.M. Depo-Provera**
Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, secondary amenorrhea, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only. 50 mg. per cc., in 1 cc. and 5 cc. vials.†

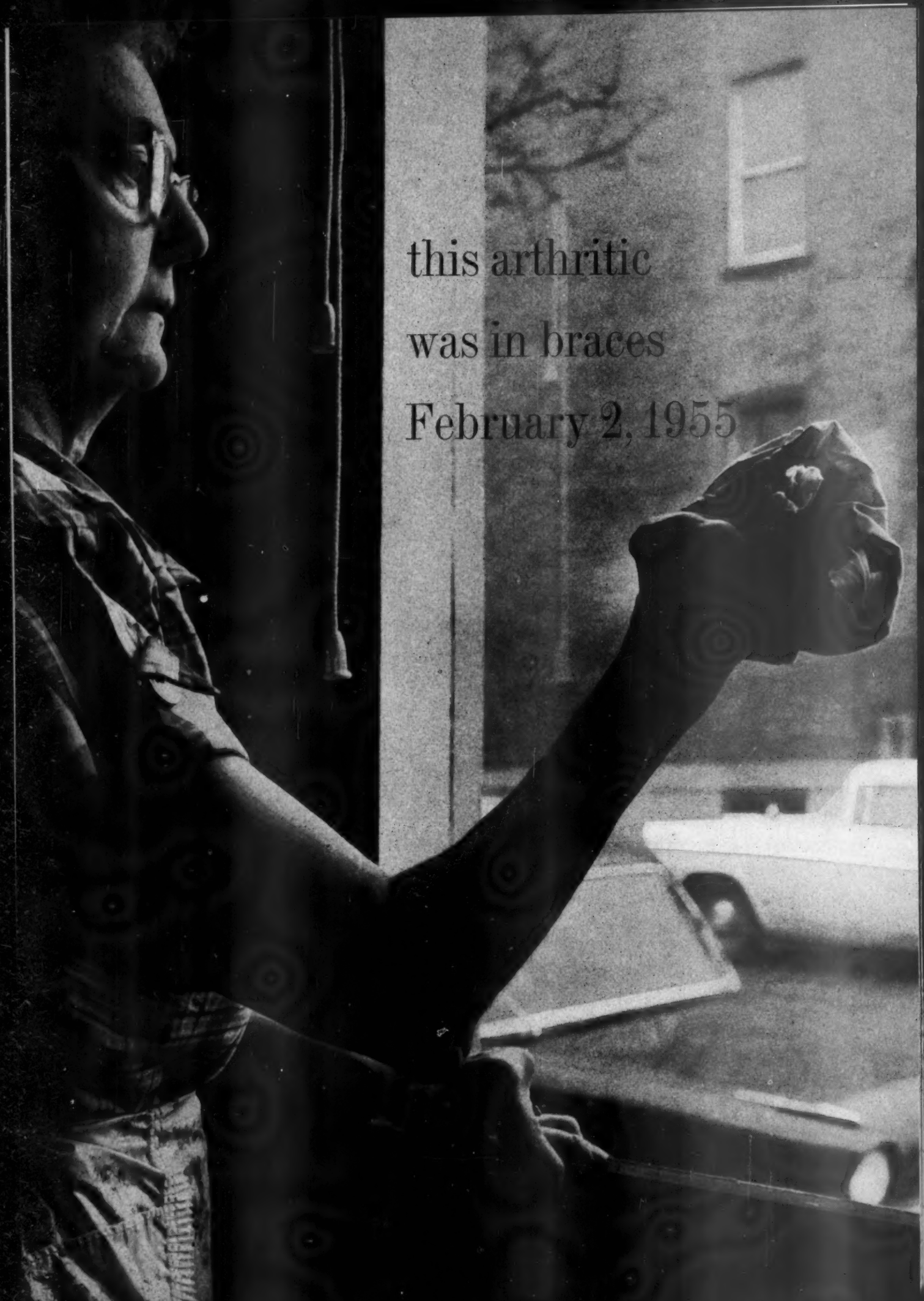
Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

*TRADEMARK, REG. U.S. PAT. OFF. **TRADEMARK


this arthritic
was in braces
February 2, 1955

Schering

maintained on Meticorten for six years she now does her own housework

H. M. first had pain in her wrists in 1940. Eventually all her peripheral joints were involved. Orthopedic surgery in 1951, 1952 and 1953 failed to restore the loss of function caused by her rheumatoid arthritis. When seen in 1954 at the age of 59, she exhibited marked deformities in her peripheral joints. Treatment with gold, phenylbutazone and cortisone had to be discontinued because of marked weight gain and moon face.



On February 2, 1955, the patient was placed on METICORTEN 5 mg. t.i.d. Eventually, she was able to discard her braces and crutches and resume a completely normal way of life. In spite of her advanced anatomical changes,



she can even use an electric mixer without discomfort.

In order to continue her improvement, she has been maintained on a dosage of 5 mg. b.i.d. In the six years since she has been on METICORTEN, the patient has had no side effects except for slight moon face and occasional purpura. As a result, she has been able to enjoy her hobbies such as crocheting and to participate in neighborhood activities.

Case history courtesy of Joel Goldman, M.D., Johnstown, Pa. These photographs of Dr. Goldman's patient were taken in her home on November 10, 1960.

METICORTEN,® brand of prednisone.

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.

JANUARY, 1961 5-796

BECAUSE POOR DIABETIC CONTROL INCREASES THE THREAT OF VASCULAR COMPLICATIONS IN DIABETES[1, 2]... DIABINESE FIRST FOR ADEQUATE AND CONTINUOUS ORAL CONTROL

Oral therapy with DIABINESE can help assure more adequate blood-sugar control in many maturity-onset diabetics, including certain patients now poorly controlled by diet alone, some patients on insulin, and many who escape control on previous oral therapy.

Diabinese and diet

In patients with maturity-onset diabetes whose blood sugar remains elevated despite weight and/or caloric control, DIABINESE is frequently effective in doses of 100 to 250 mg. a day. Further, unlike insulin, DIABINESE has not been reported to increase appetite, and residual capacity for endogenous beta cell activity is stimulated. Thus, DIABINESE combined with dietary regulation will often ensure more satisfactory control than "diet alone."

Diabinese and the insulin patient

DIABINESE has proved to be an effective replacement for insulin among maturity-onset patients needing 40 units or less per day. This application of DIABINESE is especially valuable in patients who should not be exposed to the hazards and inconvenience of self-administered injection—those with poor eyesight, the infirm and elderly, and the emotionally disturbed. Transfer from insulin to DIABINESE in proper dosage lessens the risk of hypoglycemia, and may enable certain patients to resume occupations where insulin shock is considered dangerous.

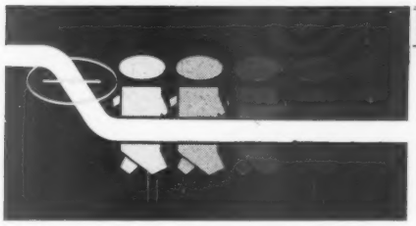
In selected patients in whom insulin requirements have become quite high, combined therapy with DIABINESE sometimes permits reduction of insulin dosage and helps to improve control.[3] Patients with insulin resistance may sometimes be similarly helped by replacement of part of the daily insulin dosage.[4]

Diabinese from the start

Continuous control in suitable candidates for sulfonylurea therapy is more likely to be achieved with DIABINESE. According to the A.M.A. Council on Drugs,[5] observations indicate that "on an equivalent dose and blood level basis, chlorpropamide has a somewhat greater therapeutic effect than has tolbutamide." This therapeutic superiority is reflected in the results of clinical observations like those of Fineberg,[6] who compared the effect of DIABINESE in 50 patients with the effect of tolbutamide in 35 patients. He concluded that "chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent)."

1. Johnsson, S.: Diabetes 9:1, 1960. 2. El Mahallawy, M. N., and Sabour, M. S.: J.A.M.A. 173:1783, 1960. 3. Editorial: Brit. M. J. 1:188, 1961. 4. Duncan, L. J. P., and Baird, J. D.: Pharmacol. Rev. 12:91, 1960. 5. A.M.A. Council on Drugs: New and Nonofficial Drugs, 1961, Philadelphia, Lippincott, 1961, p. 657. 6. Fineberg, S. K.: J. Am. Geriat. Soc. 8:441, 1960.

FOR MAXIMUM ASSURANCE OF CONTINUOUS BLOOD-SUGAR CONTROL



Diabinese®

BRAND OF CHLORPROPAMIDE

the oral antidiabetic most likely to succeed

economical once-a-day dosage

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.

Science for the world's well-being®

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc. New York 17, New York

Erythropoietin—a significant discovery in clinical hematology

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has been shown to produce reticulocytosis,[1,5-7] increase utilization of the Fe^{59} isotope, and increase erythrocyte precursors in marrow cultures.[3,8]

ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

erythropoietin levels—new criteria in diagnosis of anemia—Increased erythropoietin blood levels can be demonstrated in severe anemia and following the start of accelerated formation.[9] Soon thereafter, the effect of the higher levels appears as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? Absorption and utilization of iron are dependent upon the rate of bone marrow erythropoiesis which, in turn, is dependent upon erythropoietin levels.[11,12] Thus, the demand for iron created by accelerated erythropoiesis is satisfied by both increased gastrointestinal absorption and mobilization of storage iron. Inadequate erythropoietin levels would seemingly account for the frequently disappointing results with the use of iron alone in many of the anemias.

can medication increase erythropoietin levels? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] Cobalt-enhanced erythropoietin accelerates red cell production and improves iron utilization with a subsequent increase in hemoglobin and erythrocytes. The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF, the therapeutic cobalt-iron hematinic.

(1) Gordon, A. S.: Physiol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W.; Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Alt, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., et al.: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

For a complete background file on erythropoietin, please write to the Medical Service Department of:

V-00361-R 104-R

LLOYD BROTHERS, INC.
Cincinnati, Ohio



Povan SINGULARLY EFFECTIVE IN A SINGLE DOSE

(pyrvinium pamoate, Parke-Davis)

POVAN provides a simplified and clinically proved means of bringing a common medical problem under control. Through its unusual ability to clear most cases of pinworm infection with just one dose, POVAN permits this problem to be dealt with in a practical manner... preferably on a family or institution-wide basis.

POVAN is well tolerated... readily accepted in both dosage forms... and not appreciably absorbed through the gastrointestinal tract. Its single-dose efficacy makes therapy not only convenient, but economical as well.

Supplied: POVAN is available in suspension or tablet form. The pleasant-tasting, strawberry-flavored suspension is supplied in 2-oz. bottles and the tablets in bottles of 25.

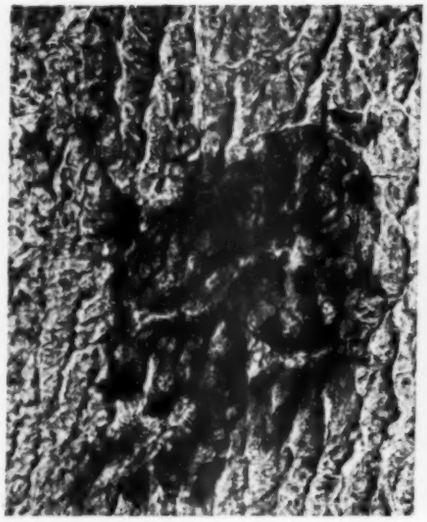


The suspension contains pyrvinium pamoate equivalent to 10 mg. pyrvinium base per cc. The sugar-coated tablets each contain pyrvinium pamoate equivalent to 50 mg. pyrvinium base. *Dosage:* Children and adults, a single oral dose equivalent to 5 mg. per Kg. of body weight. *Precautions:* Infrequent nausea and vomiting and intestinal complaints have been reported. Tablets should be swallowed whole to avoid staining teeth. Will color stools a bright red. Suspension will stain most materials.

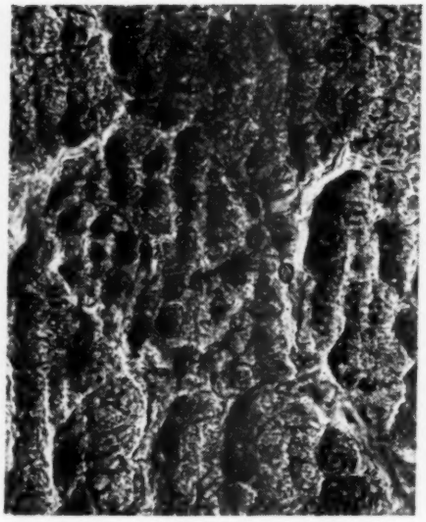
PARKE-DAVIS

65161 PARKE, DAVIS & COMPANY, Detroit 32, Michigan

Prescribe enough Orinase* to release enough native insulin



Before:
Microphotograph showing insulin granules in beta cells of pancreas of normal dog.



During:
Degranulation following administration of Orinase. Note complete release of native insulin.



After:
Regeneration of granules following termination of Orinase dosage.

Adjust Orinase dosage to make available the amount of native insulin *needed* by the diabetic patient. This may be done freely because Orinase has virtually no "ceiling" imposed on dosage by toxicity or untoward effects.

In a series of 187 diabetic patients successfully managed on Orinase (tolbutamide) during a period of 6 to 30 months, the reported[1] distribution of daily doses was as follows: 1 gram, 17%; 1.5 grams, 22%; 2 grams, 40%; 3 grams, 21%.

Similarly, in three years' clinical experience with a population of approximately 3,000 diabetics on Orinase, it has been observed that about one-third of the patients at any one time require and receive dosages of 2 to 3 grams a day for successful management.[2]

To obtain optimum control, and avoid needless "secondary failures"—give sufficient Orinase to meet varying requirements from patient to patient or in a given patient from time to time.

Each tablet contains:
Tolbutamide . . . . . 0.5 Gm.

1. Gorman, C. K., and Weaver, J. A.: Brit. M. J. 2:1214 (Dec. 5) 1959.
2. Case data courtesy Henry Dolger, M.D.

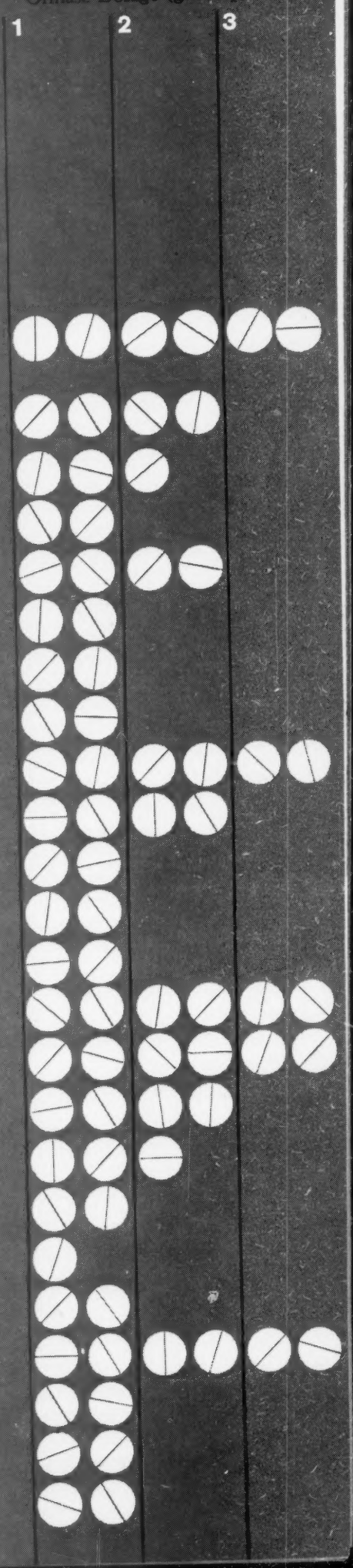
*TRADEMARK, REG. U. S. PAT. OFF.—TOLBUTAMIDE, UPJOHN

Upjohn

THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

a three-year case history[2]

Date	Entries and Comments
6/21/56	Mr. J. S., 54 yrs. old, diabetes mellitus 1½ yrs. F. H.—neg. for diabetes. P. H.—surg. 0, med. 0. Restaurant manager—M., 3 children living and well. Wt. 155 lb. 1 yr. ago; now 125. P. I.—onset 1½ yrs. ago with thirst and polyuria; glycosuria found. On diet. In past year lost 30 lb., strict diet—all kinds of dietetic substitutes. Some asthenia. Afraid of insulin. No recent glycosuria or nocturia. P. Exam.—thin male. Fundi neg. ENT neg. BP 140/80. Heart and lungs neg. Extremities: poor pulses. Urine—sugar 0, acetone 0. Noon blood sugar 240. Rx more adequate diet and Orinase 3 Gm.
7/9/56	Wt. 127, urine 0-0. B. S. 110, occ. nocturia but no glycosuria. Rx: eat more, Orinase 2 Gm.
8/29/56	Wt. 139½, urine 0-0-0. B. S. 205. Rx 1.5 Gm.
10/1/56	Wt. 143, urine 0-0-0. B. S. 125. Rx 1 Gm.
11/5/56	Wt. 148, urine 4+ -0-0, noon B. S. 160. Rx 2 Gm.
12/7/56	Wt. 146, urine 0-0-0, noon B. S. 120. Rx 1 Gm.
1/11/57	Wt. 144½, urine 0-0-0, noon B. S. 150. Rx 1 Gm.
3/11/57	Wt. 144½, urine 0-0, noon B. S. 120. Rx 1 Gm.
5/10/57	Wt. 140½, urine 4+ -0-0. B. S. 275. Rx 3 Gm.
6/12/57	Wt. 138½, urine 0-0-0, noon B. S. 114. Rx 2 Gm.
8/7/57	Wt. 136½, urine 0-0-0. B. S. 100. Rx 1 Gm.
10/2/57	Wt. 136½, urine 0-0-0. B. S. 85. Rx 1 Gm.
11/29/57	Wt. 136½, urine 0-0-0. B. S. 128. Rx 1 Gm.
1/17/58	Wt. 134¼, urine 4+ -0-0. B. S. 216. Rx 3 Gm.
2/14/58	Wt. 132, urine 0-0-0. B. S. 135. Rx 3 Gm.
3/28/58	Wt. 136½, urine 0-0-0, noon B. S. 93. Rx 2 Gm.
5/5/58	Wt. 138, urine 0-0-0. B. S. 112. Rx 1.5 Gm.
6/16/58	Wt. 137, urine 0-0-0. B. S. 93. Rx 1 Gm.
8/11/58	Wt. 138, urine 0-0-0, noon B. S. 132. Rx 0.5 Gm.
10/20/58	Wt. 134, urine 3+ -0-0. B. S. 220. Rx 1 Gm.
11/24/58	Wt. 131½, urine trace -0-0. B. S. 251. Rx 3 Gm.
2/18/59	Wt. 134, urine 0-0-0. B. S. 120. Rx 1 Gm.
4/9/59	Wt. 137½, urine 0-0-0. B. S. normal. Rx 1 Gm.
6/5/59	Wt. 138, urine 0-0-0. B. S. normal. Rx 1 Gm.



a pair of cardiac patients:



both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

▲ by mouth ▲ by needle ▲ by rectum

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.

KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY

only 2 seconds to specify MAXIMUM QUALITY

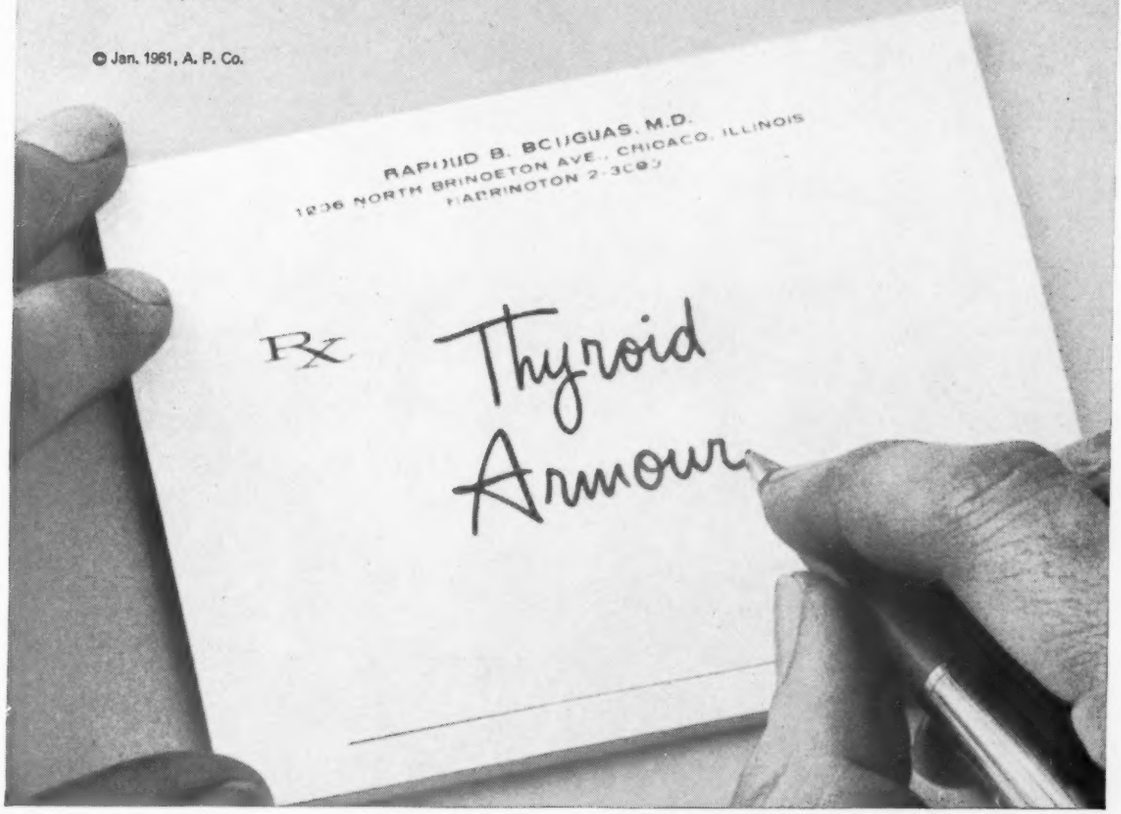
It takes only 2 seconds to specify "THYROID ARMOUR" on a prescription blank, yet these words represent the highest grade thyroid available, manufactured with all the control skills learned during three-quarters of a century of experience with endocrine products. THYROID ARMOUR is the original standard of comparison for all thyroid preparations, and is regarded throughout the world as the quality thyroid product.

THYROID U.S.P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (non-toxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved, i.e., gynecologic conditions such as functional menstrual disorders, sterility, habitual abortion; recurring conjunctivitis; certain types of anemias and obesity; and certain changes which occur in hair, skin and fingernails. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger: potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz. 4 oz., and 1 lb. bottles.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS *Armour Means Protection*

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"If of thy mortal goods thou art bereft,
And from thy slender store two loaves alone to thee are left,
Sell one, and with the dole
Buy hyacinths to feed thy soul."
-Muslih-ud-Din Saadi

Upjohn

75th year

Man does not live by bread alone.
If he did, medicine would be purely a science, concerned only with "bread to nourish the body."

Thoughtful physicians have long recognized the equal essentiality of "hyacinths to feed the soul." This is the *art* of medicine.

If yours is a typical practice, many of the patients who come to you have no demonstrable somatic pathology. Yet their symptoms often are myriad: low back pain, recurrent headaches, insomnia, anorexia, chronic fatigue, apathy, inability to concentrate, "blues."

Most of these patients are not candidates for psychiatry, and certainly not for tranquilizers or sedatives. They are candidates for the simple psychomotor effect of Monase. Tests in more than 2,000 such patients justify the expectation that Monase will enable many of these patients to sleep better, eat better, and feel better.

For the 4 out of 10 patients with no demonstrable pathology,† consider

Monase*



*TRADEMARK, REG. U.S. PAT. OFF.
†ESTIMATED AVERAGE IN GENERAL PRACTICE
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Description: Monase is etryptamine acetate, a unique non-hydrazine compound, developed in the Upjohn Research Laboratories.

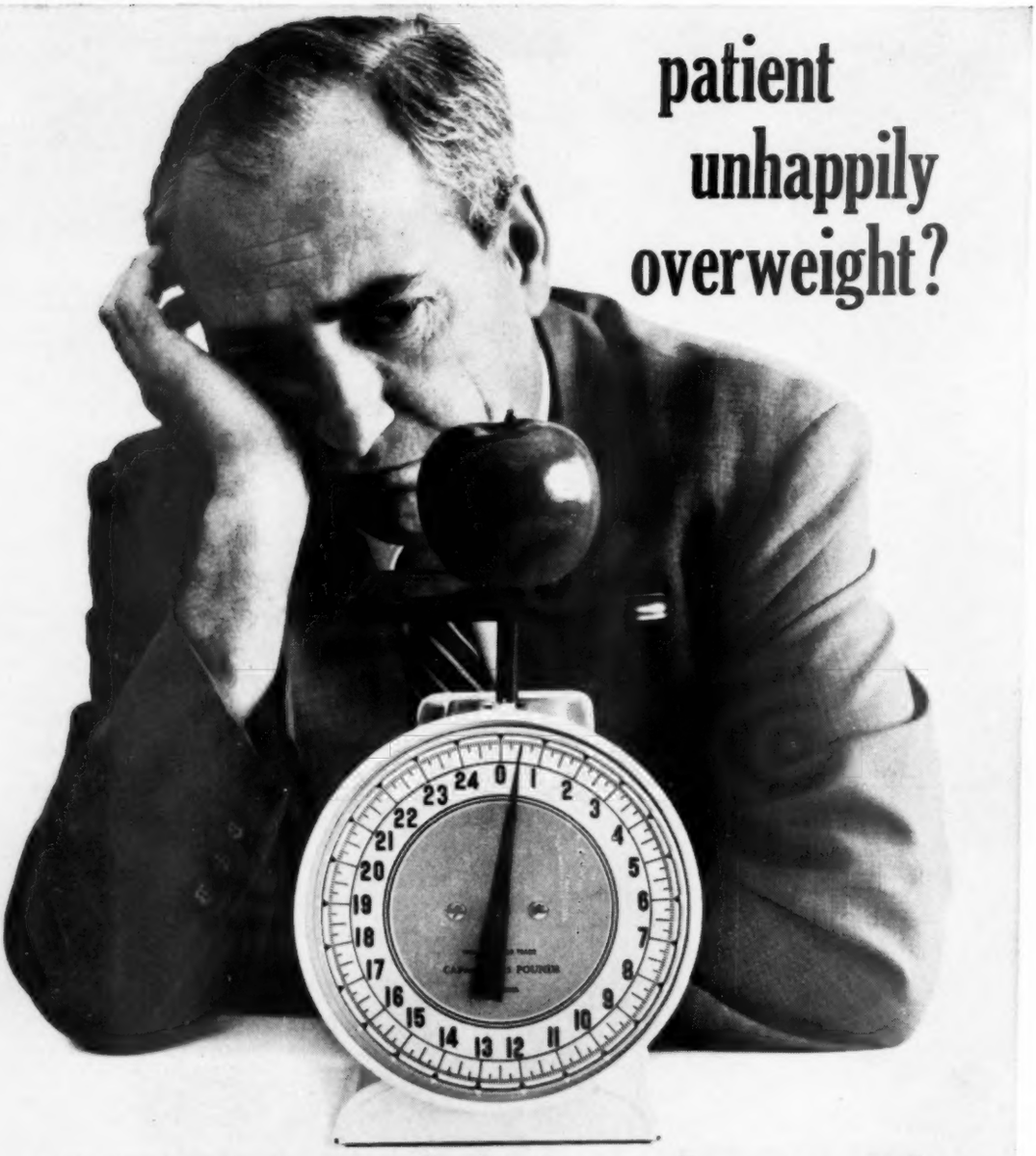
Indications: Various depression states: manic-depressive reaction, depressed type; involutional psychotic reactions with depressed features; psychotic depressed reactions; psychoneurotic depressive reactions; psychiatric disorders with prominent depressive symptoms or features; transient situational personality disorders with pathological depressive features.

Dosage: 30 mg. daily in divided doses. Initial benefit may be observed within 2-3 days, but maximum results may not be apparent until after 2 or more weeks. Adjustment of dose to individual response should be effected in increments or decrements of 15 mg. daily at weekly intervals. The daily maintenance dose ranges between 15 and 45 mg. In schizophrenics, 30 mg. daily may be useful as an adjunct in activating these patients or brightening their mood.

Contraindications and Precautions: There are no known absolute contraindications to Monase therapy. However, the drug should be used with caution in schizoid or schizophrenic patients, paranoids, and in patients with intense anxiety, as it may contribute to the activation of a latent or incipient psychotic process. Patients with suicidal tendencies should be kept under careful observation during Monase therapy until such time as the self-destructive tendencies are brought under control.
Patients who are on concomitant antihypertensive therapy should be watched carefully for possible potentiation of hypotensive effects. Added caution should be employed in patients with cardiovascular disease in view of the occasional occurrence of postural hypotension, and the possibility of increased activity as a result of a feeling of increased well being.
Despite the fact that liver damage or blood dyscrasias have not been reported in patients receiving Monase, as is the case with any new drug, patients should be carefully observed for the development of these complications. Monase should probably not be used in patients with a history of liver disease or abnormal liver function tests. Also the usual precautions should be employed in patients with impaired renal function, since it is possible that cumulative effects may occur in such patients.
Monase should be employed with caution in patients with epilepsy since the possibility exists that the epileptic state may be aggravated. Also because of its autonomic effects, therapy with Monase may aggravate glaucoma or may produce urinary retention. Monase must not be administered concomitantly with imipramine. In patients receiving Monase caution should be employed in administering the following agents or related compounds in view of possible lowering of the margin of safety: meperidine, local anesthetics (procaine, cocaine, etc.), phenylephrine, amphetamine, alcohol, ether, barbiturates or histamine.

Toxicity and Side Effects: The side effects observed in patients on Monase therapy in general have been mild and easily managed by symptomatic therapy or dose reduction. If such side effects persist of are severe, the drug should be discontinued. Alterations in blood pressure, usually in the form of postural hypotension, or more rarely, an elevation of blood pressure have been reported. Other side effects include allergic skin reactions and drug fever and those that appear to be dose related since they are more likely to occur when the daily dose exceeds 60 mg. These are nausea and gastrointestinal upset, headache, vertigo, palpitation, dryness of the mouth, blurred vision, over-stimulation of the central nervous system, restlessness, insomnia, paradoxical somnolence and fatigue, muscle weakness, edema, and sweating. Following sudden withdrawal of medication in patients receiving high doses for a prolonged period. There may occur a "rebound" withdrawal effect which is characterized by headache, central nervous system hyperstimulation and occasionally hallucinations.

Supplied: Monase, compressed tablets, 15 mg. in bottles of 100.



patient unhappily overweight?

minimize care and eliminate despair with

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brand Methamphetamine Hydrochloride

Controls food craving, keeps the reducer happy—In obesity, "our drug of choice has been methedrine . . . because it produces the same central effect with about one-half the dose required with plain amphetamine, because the effect is more prolonged, and because undesirable peripheral effects are significantly minimized or entirely absent."[1] Literature available on request.

Supplied: Tablets 5 mg., scored. Bottles of 100 and 1000.

[1] Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

what TWISTON does for your allergy patient

TWISTON®

rotoxamine

takes him out of this class: zzzzzzzzzz zzzzzzzzzzzzzz zzzzzzzzzzzzzz

puts him into this class: !!!!!!!!!!!!!!! !!!!!!!!!!!!!!!!!!!!!!!!!!!!! !!!!!!!!!!!!!!!!!!!!!!!!!!!!!

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. . . anti-side effects

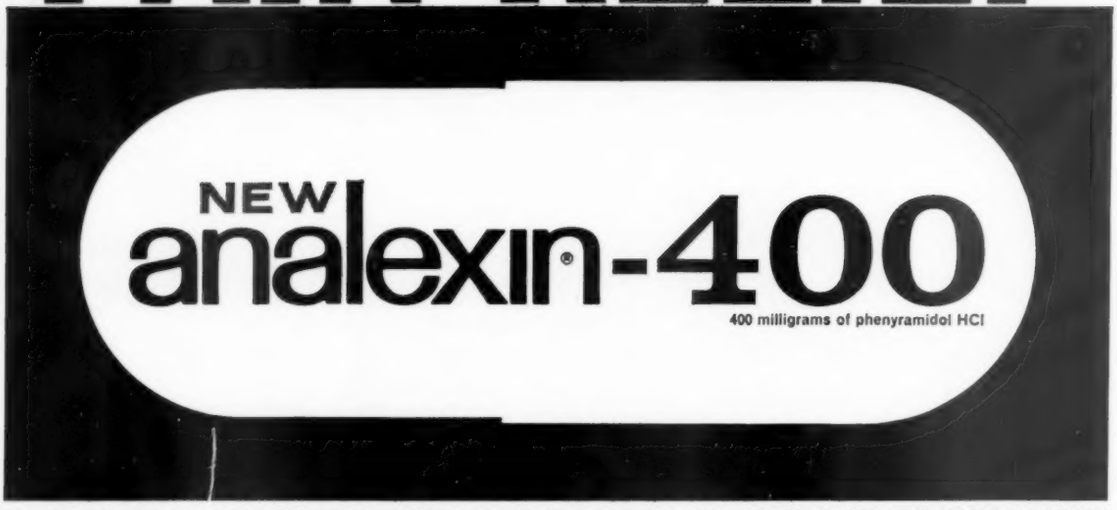
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PAIN RELIEF



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EXCEEDINGLY EFFECTIVE ". . . The 85.1% incidence of effectiveness with the 400 mg. dose has exceeded the analgesic effectiveness of any other analgesic agent which we have studied to date, either alone or in combination. . . . The utilization of higher doses for short periods of time indicates that the medication has a large therapeutic range, and this is reflected in the high incidence of effectiveness and low likelihood of untoward reactions.

"The practicing physician translating this into his own needs may be completely confident of using a medication with an excellent predictability and a safe analgesic response."[1]

EXTRAORDINARY MARGIN OF SAFETY. *Analexin-400 is non-narcotic and not narcotic related;* thus, it presents no danger of habituation or any other reaction associated with the frequent use of narcotics. Nor will Analexin-400 produce sedation, mental confusion or depression occasionally observed with other analgesics or interneuronal blocking agents.[1-23]

INDICATIONS: Relief of pain in injury, low back pain, premenstrual cramping, dysmenorrhea, postoperative pain, and a wide variety of recurring and acute painful conditions.

DOSAGE: One capsule at onset of pain, followed by 1 capsule at intervals of 1 to 4 hours, as needed.

REFERENCES: From the Symposium, *Recent Concepts of Pain and Analgesia*, held in the Hall of States, American Hospital Association, Chicago, February 15, 1961: 1. Batterman, R. C.: *Non-Narcotic Analgesia in Ambulatory Patients.* 2. O'Dell, T. B.: *Experimental Parameters in the Evaluation of Analgesics.* 3. Miller, L. D.: *Distribution, Excretion and Metabolic Fate of Phenyramidol.* 4. Beisler, E.: *Preliminary Report of Experience with Phenyramidol for Dental Analgesia.* 5. Bader, G.: *Preliminary Report on the Use of Analexin for Dysmenorrhea in Telephone Operators.* 6. Taylor, S. L.: *Phenyramidol in General Hospital Orthopedics.* 7. Bodi, T.: *Pain Management Among Clinic Outpatients.* 8. Ramunis, J.: *Experience of an Industrial Surgeon with Phenyramidol.* 9. Kast, E. C.: *Methodological Considerations in the Clinical Evaluation of an Analgesic.* 10. Collopy, C. T.: *Preliminary Comparisons of Two Non-Narcotic Analgesic Agents in Hospitalized Orthopedic Patients.* 11. Cass, L. J.: *Report on the Analgesic and Calmative Effectiveness of Two Preparations on Patients with Acute and Chronic Pain.* 12. Lamphier, T. A.: *Intravenous Phenyramidol in the Management of Low Back Pain and Allied Disorders.* 13. O'Dell, T. B.: Chicago Med. *63*:9, 1961. 14. Kast, E. C.: Chicago Med. *63*:17, 1961. 15. Wainer, A. S.: J. Am. M. Women's A. *16*:218, 1961. 16. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 17. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 18. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 19. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 20. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 21. Wainer, A. S.: Clin. Med. *7*:2331, 1960. 22. Clinical data in files of Medical Dept., Irwin, Neisler & Co., 1959. 23. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

ANOTHER ACHIEVEMENT OF NEISLER RESEARCH **IRWIN, NEISLER & CO.** 75th year DECATUR, ILLINOIS

to combat the three-pronged assault of urinary tract infections — bacteriuria — tissue infection — discomfort

UROBIOTIC®

COSA-TERRAMYCIN®—SULFONAMIDE—ANALGESIC

Only **UROBIOTIC** *contains:* **OXYTETRACYCLINE** (with glucosamine for enhanced absorption) — notable for its wide tissue distribution, high urinary concentration, excellent toleration and proven antibiotic effectiveness against even so troublesome an invader as *Pseudomonas;* **SULFAMETHIZOLE** — an unusually soluble, highly active sulfonamide; **PHENYLAZO-DIAMINO-PYRIDINE** — for effective local analgesia.

IN BRIEF

INGREDIENTS: Each Urobiotic capsule contains 125 mg. Terramycin® (oxytetracycline) with 125 mg. glucosamine HCl, 250 mg. sulfamethizole, and 50 mg. phenylazo-diamino-pyridine HCl.

INDICATIONS: Urobiotic is indicated in the treatment of a number of common genitourinary infections caused by susceptible organisms. It may also be used prophylactically before and after genitourinary or pelvic surgery, following instrumentation procedures, during the use of retention catheters, and in patients with conditions such as cord bladder or cystocele.

DOSAGE: In adults, a dose of 1 or 2 capsules four times daily is suggested, depending upon the severity and response of the infection. In children 60 to 100 lbs., the suggested average dose is 1 capsule four times daily; in children under 60 lbs., 1 capsule three times daily. Therapy should be continued for a minimum of 7 days or until bacteriologic cure is effected in acute urinary tract infections.

CONTRAINDICATIONS: Urobiotic may be contraindicated in patients with chronic glomerulonephritis, hepatitis, hepatic failure, uremia, and obstructive lesions of the urinary tract, and should not be used in patients sensitive to any of its components.

PRECAUTIONS: The use of broad-spectrum antibiotics may, in rare cases, result in an overgrowth of nonsusceptible organisms, such as monilia or staphylococci. Should such superinfection occur, therapy with Urobiotic should be discontinued and specific therapy instituted as shown by susceptibility testing. The use of sulfonamides may cause renal crystalluria or skin rash, as well as other toxic or sensitivity reactions. If any of these occur, discontinue use.

SUPPLIED: Urobiotic capsules, yellow-and-grey, bottles of 50.

Pfizer

More detailed professional information available on request.

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ONLY QUINAGLUTE® DURA-TAB S.M.® PROVIDES ORAL QUINIDINE GLUCONATE (5 gr.) ...BETTER TOLERATED



because it is 10 times as soluble as the sulfate

SAMPLES and literature—write... REFER TO PDR Page 821

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*U.S. Patent 2,895,881

in q. 12 h. dosage each Sustained Medication* dose maintains uniformly effective, virtually non-fluctuating blood levels, all day, all night.

in cardiac arrhythmias for maximum quinidine efficacy, tolerance, convenience[1-5]—specify Quinaglute Dura-Tab S.M. Bottles of 30, 100 and 250.

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957. 2. Bellet, S.: Amer. Heart J. 56:479, 1958. 3. Bellet, S.: Amer. J. Cardiology 4:268, 1959. 4. Finkelstein, D.: Penn. Med. J. 61:1216, 1958. 5. DiPalma, J. R.: Progress in Cardiovascular Dis. 2:343, 1960.

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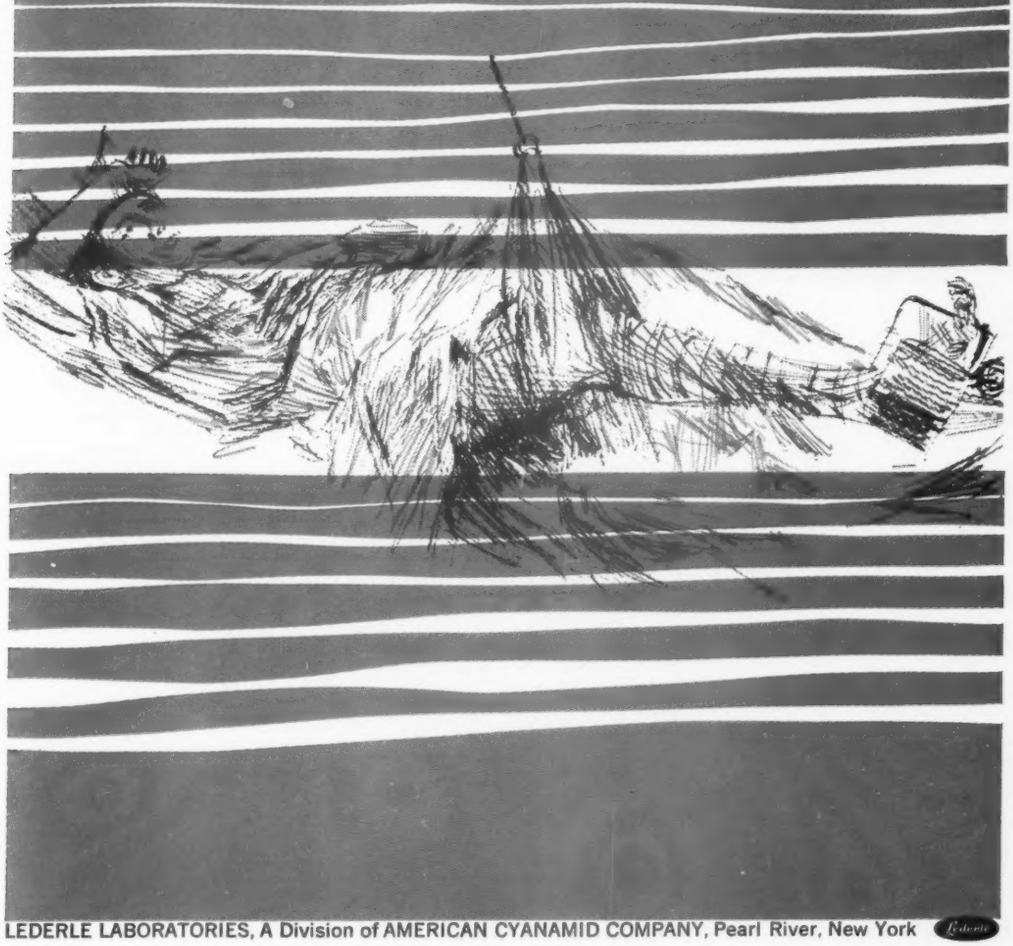
Packaged (30 and 100) in decorative "reminder" jars.

Each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Calcium Pantothenate	20 mg.

Average dose: 1 to 2 capsules daily.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.



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with calcium iodide

You've seen the type. Racked by a chronic cough . . . or wheeze . . . or any of the other classic asthma symptoms. In any event, the usual treatment isn't affording adequate relief.

If you're faced with this kind of "problem" patient, try this: Put him on Norisodrine Syrup for two weeks—one or two teaspoonfuls, four to six times daily. See if this isn't evident:

Coughing will be more productive . . . and much less frequent. There will be a marked lessening of tension, physical and mental. Respiration will improve. Nighttime cough, particularly, will be relieved.

Good-tasting Norisodrine Syrup—a combination of Norisodrine (bronchodilator) and calcium iodide (expectorant)—can help you control symptoms in patients of all ages, even those who have been troubled for years.

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it is
effective

The continuing clinical effectiveness of Terramycin therapy derives as always from its proven antibiotic characteristics—rapid absorption; notably wide distribution in body tissues and fluids; high, active urinary concentrations; and a broad anti-infective spectrum embracing even such a troublesome organism as Pseudomonas. Additionally, Terramycin therapy provides the assurance of a 10-year record of exceptional toleration.



Cosa-Terramycin®

OXYTETRACYCLINE WITH GLUCOSAMINE

today's oral *form of Terramycin*

IN BRIEF

Cosa-Terramycin provides oxytetracycline (Terramycin®) with glucosamine for maximum absorption.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms), Cosa-Terramycin is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: Adults: 1 Gm. of oxytetracycline daily in four divided doses is usually effective. In *severe* infections, a larger dosage (2-4 Gm. daily) may be indicated. Infants and children: 10-20 mg. of oxytetracycline per lb. of body weight daily. Certain diseases are treated in courses.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms—particularly monilia and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terramycin Capsules,* 250 mg. and 125 mg. Terramycin is also available in: *Cosa-Terrabon® Oral Suspension,* a palatable preconstituted aqueous suspension containing 125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; *Cosa-Terrabon® Pediatric Drops,* a palatable preconstituted aqueous suspension containing 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper; and *Terramycin Intramuscular Solution, conveniently preconstituted,* in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

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after eleven million treatment courses*...

through the years... consistently broad antibacterial action against urinary tract pathogens

"It was interesting to observe that nitrofurantoin [FURADANTIN] showed a consistent in vitro effectiveness against the bacteria tested throughout the four year period, thus revealing negligible development of bacterial resistance, if any, through the years."[1]

*Conservative estimate based on the clinical use of FURADANTIN tablets and Oral Suspension since 1953.



consistently broad antibacterial action

"...was given continuously and safely for as long as three years."[2]

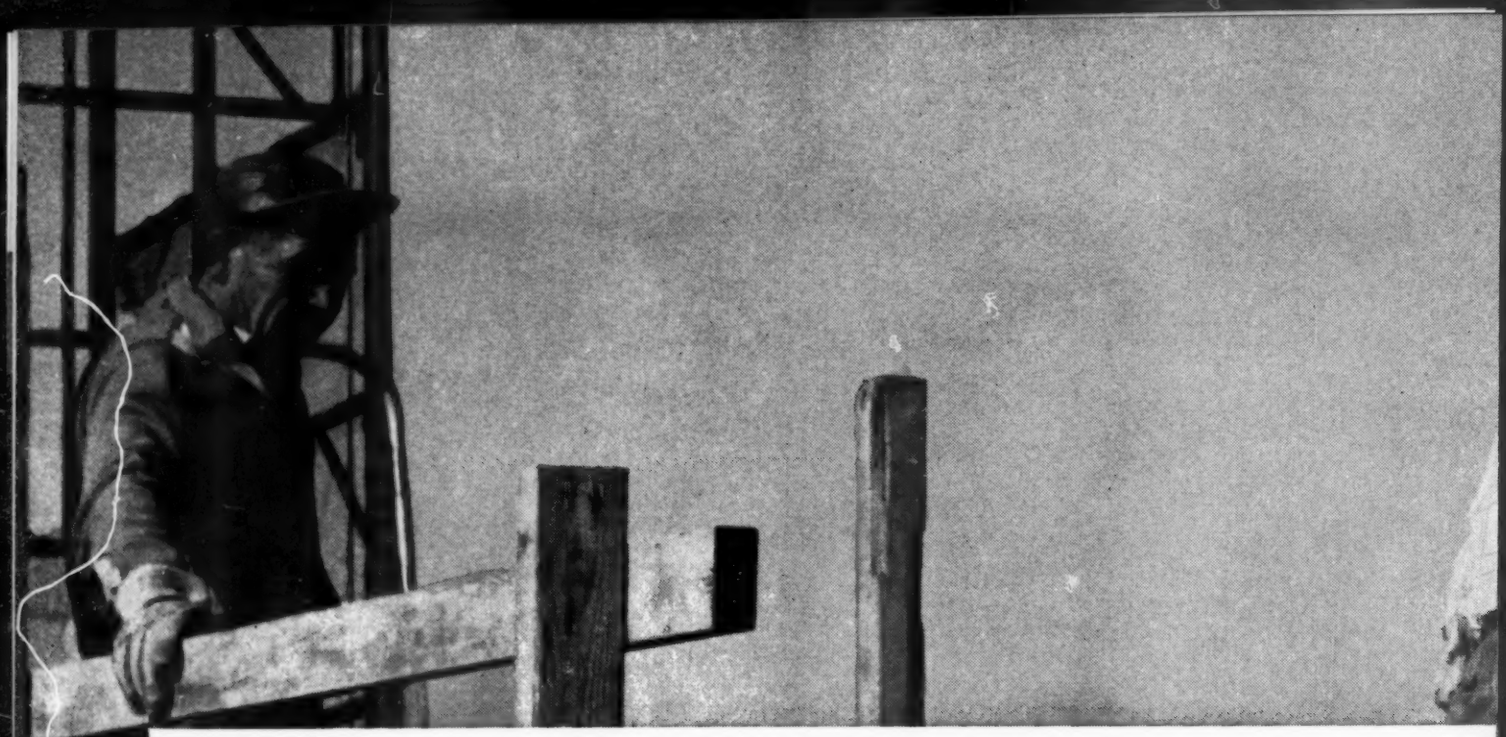
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brand of nitrofurantoin

rapid, safe control of infection throughout the urinary system

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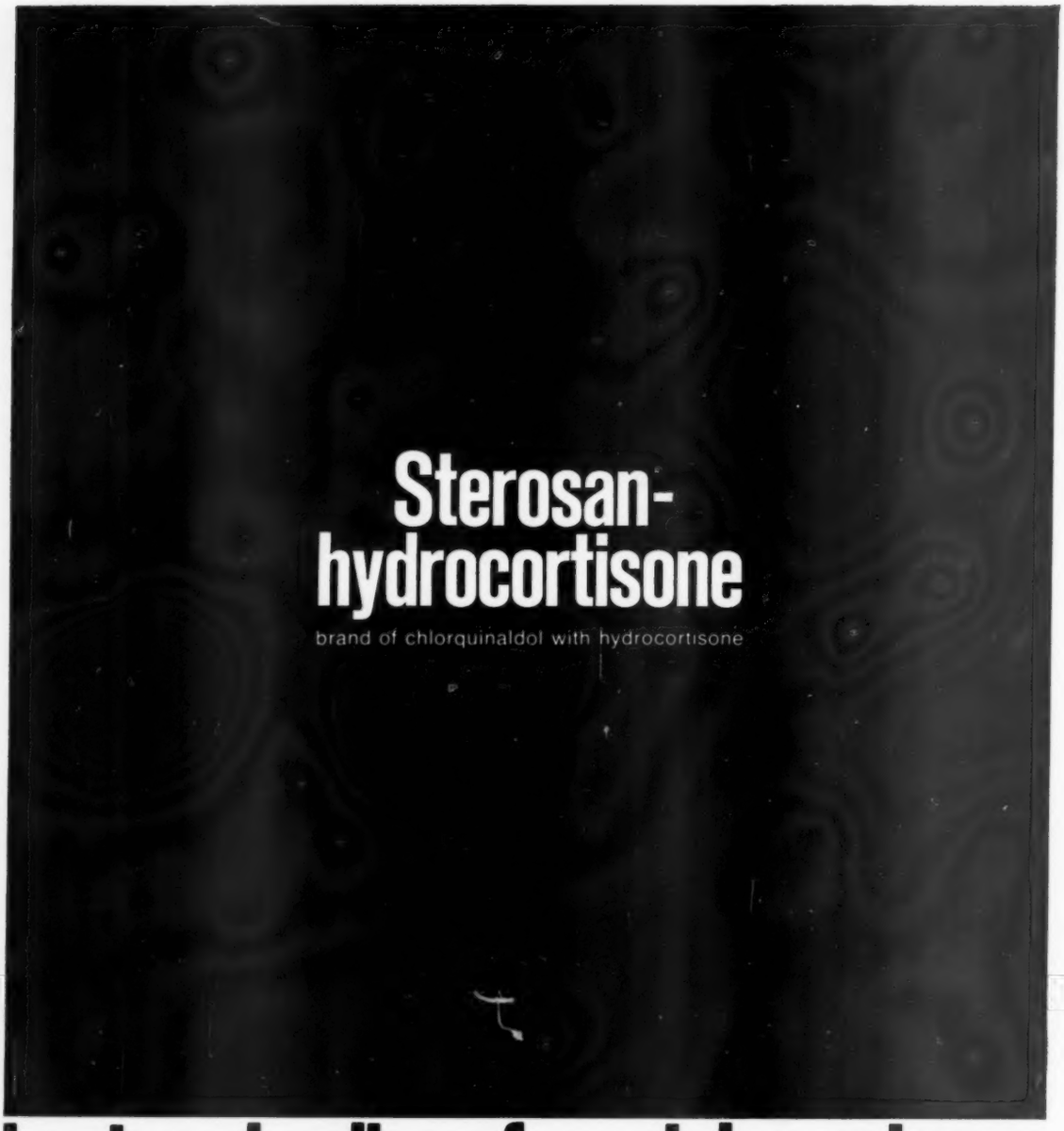
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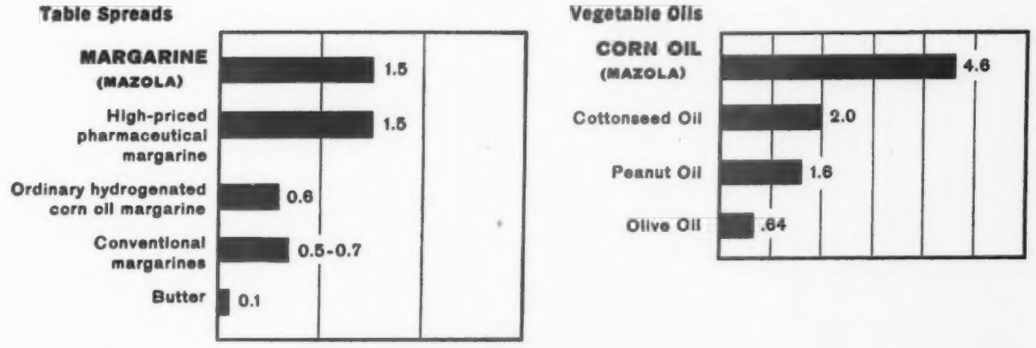
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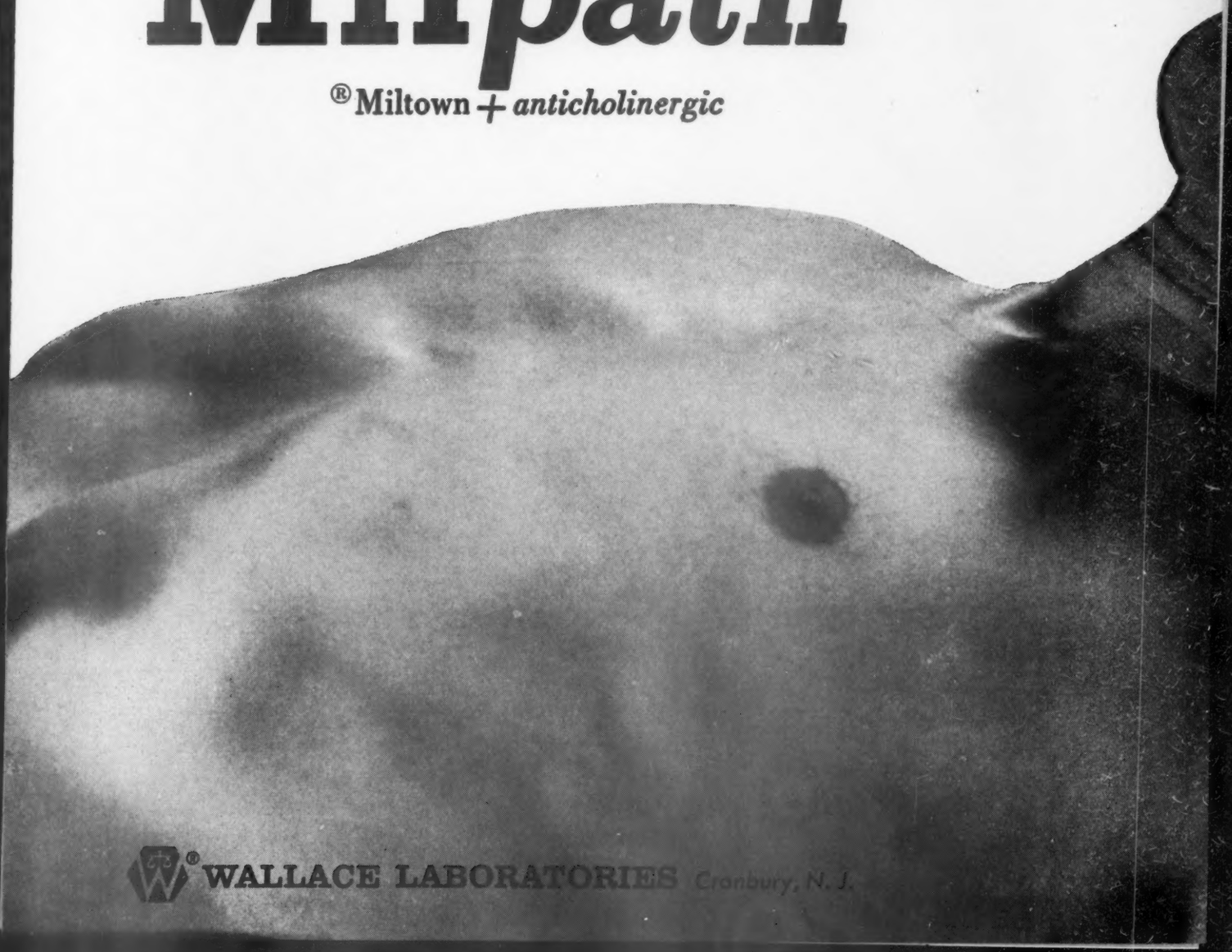
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Editorial

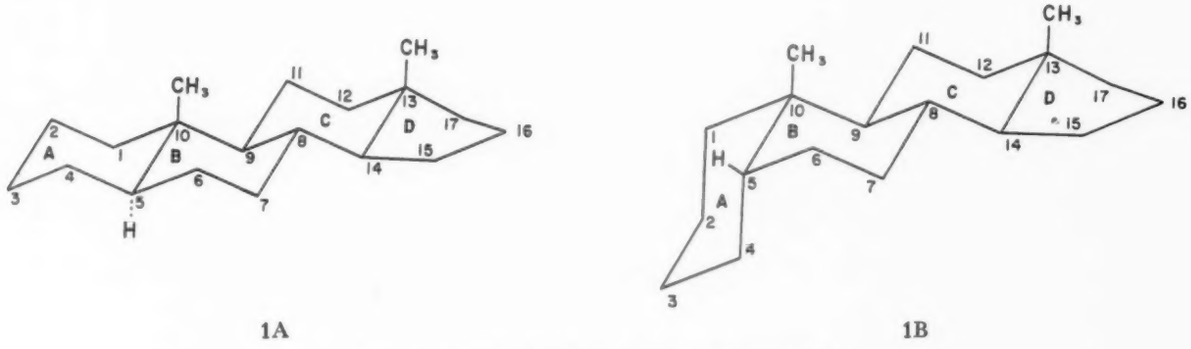
Steroid Fever*

IT has generally been assumed that the structural alterations which adrenocortical and gonadal steroid hormones undergo during their metabolism *in vivo* "inactivate" these substances and that the numerous metabolites which derive from these hormonal degradations represent "waste products" devoid of significant physiologic activity. Recent studies demonstrating the fever-producing action of steroid metabolites in man, however, disaffirm this view and indicate that the chemical transformations which steroid hormones undergo *in vivo* may result in the formation of new derivatives possessing novel and potent forms of biological action which may find clinical expression.

The thermogenic properties of 5β-H† steroid metabolites in man were first reported in 1956; subsequent studies have confirmed the intense pyrogenic activity of these compounds and

† The non-benzenoid steroid hormones, i.e., all those except the estrogens, are characterized structurally by a conjugated ketone and double bond system at carbons 3, 4 and 5 of ring A of the steroid nucleus. Enzymatic reduction of the C4-5 double bond yields two major isomeric series of metabolites which are named according to the nature of the resultant A:B ring closure. In the 5α-H series, the hydrogen atom attached to carbon 5 projects to the rear plane of the nucleus and C19 and C21 metabolites are called, respectively, androstane and allopregnane compounds. In the 5β-H series, the C5 hydrogen projects to the frontal plane of the nucleus as does the methyl group at carbon 10, and the comparable C19 and C21 metabolites are etiocholane, or pregnane derivatives.

The nature of the A:B ring juncture is quite different in these two series of derivatives, as indicated by the stereochemical models in Figure 1. In these C19 models, for purposes of simplification, only the orientations of the methyl groups at C10 and C13 and the hydrogen atom at C5 are indicated.



1A 1B

FIG. 1. A, 5α-H (A:B *trans*). B, 5β-H (A:B *cis*).

* This study was supported in part by the Joseph and Helen Regenstein Foundation. Manuscript received April 21 1961.

defined certain aspects of the structural and species specificity of their action [*1–9*]. The C19 steroid, etiocholanolone, may be considered a chemical and pharmacologic prototype of this new class of pyrogens, although a number of related C21 and C24 steroids such as pregnanolone, pregnandiol, 11-ketopregnanolone and lithocholic acid also exhibit fever-producing activity [*10*]. The characteristics of the thermogenic reaction which these compounds provoke in man have been described in detail but the mechanism by which they act to produce fever remains unclear [*7,10*]. Previous studies on the pathogenesis of fever have generally utilized the pyrogenic response of animals to injection of products of bacterial and viral origin as an experimental prototype of clinical fever, and by this means the probable mechanisms of several forms of experimental and natural microbial fevers have been elucidated [*11,12*]. The species specificity of fever induced by steroid metabolites has prevented comparable investigation of this phenomenon in laboratory animals [*8,9*]. However, studies in human subjects have revealed a number of differences in the biological properties of bacterial and steroid pyrogens, including the species specificity of steroid pyrogen action already noted; the prolonged latent period of fever provoked by steroids compared with that induced by bacterial endotoxins; and the apparent absence of a circulating transferable pyrogenic substance in the plasma of patients with steroid fever comparable to the leukocyte or "endogenous pyrogen," which is released into the bloodstream of animals during the course of bacterial endotoxin-induced fever [*13–19*]. These physiologic differences have been interpreted as implying that these two classes of pyrogenic substances may provoke fever by somewhat different modes of action [*10*]. Whether or not these distinctions do in fact prove to be pertinent to the mechanism of steroid fever, this phenomenon has important physiologic and clinical implications.

The physiologic significance of steroid fever lies in the demonstration that this biological reaction can be consistently provoked in man by hormonal degradation products, a class of endogenous compounds which has generally been thought to be physiologically inert. By inference, the probable existence of new and previously unsuspected biological activity in other substances considered to be inactive "waste products" of hormone metabolism in man may be anticipated. That this suggestion already has considerable foundation in fact is indicated by a number of observations. Thus, certain steroid metabolites or related compounds have powerful hypnotic and anesthetic properties [*20–22*]; the antibiotic and tumor-inhibitory effects of steroid hormone derivatives are well known [*23–25*]; the metabolic activity of progesterone metabolites has been demonstrated [*26*]; the potent hypocholesterolemic action of androsterone has recently been recognized [*27*]; and a number of steroid metabolites have been shown capable of participating as coenzymes in hydrogen transport mechanisms by various dehydrogenases [*28,29*]. Of special interest and importance is the fact that hormonal metabolites may possess biological properties unlike or antagonistic to those exhibited by their precursor hormones [*6*], since interaction of the physiologic effects of primary glandular secretions with those of their *in vivo* derivatives could have considerable influence on the ultimate expressions of hormone action in man. Further study of the physiologic and pharmacologic properties of hormonal transformation products, especially in man, would thus appear to be a potentially fruitful area of investigation.

The clinical significance of steroid fever follows from the fact that pyrogenic steroids constitute a new chemical class of thermogenic agents of natural origin. The number and structural diversity of these compounds suggests that the term "endogenous pyrogen" may have general rather than specific meaning [*12*] and the physiologic source of these pyrogenic substances naturally stimulates interest in their possible participation in the mechanism of fever generally. That this interest is more than speculative is indicated by the studies of Bondy et al. [*30*] who in 1958 reported the presence of the steroid pyrogen, etiocholanolone, in the plasma of two patients during the febrile phase of "periodic fever" [*31*], and its disappearance from plasma during the afebrile course of this episodic disease. This observation was confirmed in a larger series of patients with this disorder in 1960 [*32*], and it was noted that comparable high levels of this steroid pyrogen were not present in the plasma of control patients with microbial fever. Elevated plasma levels of unconjugated etiocholanolone have also been suspected or observed in certain febrile patients with cirrhosis of the liver [*33*] and primary adrenocortical disease [*34*]. Since chemical esterification of steroid pyrogens such as etio-

cholanolone or pregnanolone abolishes their thermogenic activity [7], it has been suggested that hepatic conjugation of steroids may be partially defective in these clinical disorders. However, recent studies from these laboratories [35] indicate that, unlike the esters of neutral steroid pyrogens, physiologic and chemical conjugates of the endogenous biliary steroid pyrogen, lithocholic acid, have marked fever-producing activity in man. Thus *in vivo* esterification does not *necessarily* terminate the biological activity of steroids, and attention must also be focused on extrahepatic processes in examining the pathologic basis of fevers suspected to be of steroidal origin. The enzymatic properties exhibited by certain blood proteins which lead to the selective formation of 5β-H stereoisomers from C19 and C21 steroid precursors [36] may typify one such potential extrahepatic mechanism for steroid pyrogen formation *in vivo*.

The name "etiocholanolone fever" has been applied to the variant of periodic disease studied by Bondy and associates, although the problems related to early specific etiologic classification in this field have been noted [32]. There may be some present value in the use of a more general descriptive term such as "steroid fever," however, since this designation does not exclude participation of other thermogenic steroids in the pathogenesis of periodic fever or related diseases —a possibility which is inherent in the large number of pyrogenic compounds of this type which have already been described. These studies in periodic fever [30,32,37] represent a significant advance which confirms the participation of this new class of endogenous pyrogenic substances in the mechanism of fever and suggests the importance of investigating the possible role of other steroid pyrogens in physiologic or pathologic temperature elevation [6,10]. At the present time, studies of this type are hindered by the lack of simple and accurate methods for the detection and quantitative analysis of these compounds in biological fluids. Intensive efforts directed towards the development of such precise technics would appear warranted, since detailed qualitative and quantitative studies of plasma steroids in febrile patients may demonstrate that a variety of steroid pyrogens of endogenous origin participate actively in the pathogenesis of many forms of periodic, recurrent or prolonged fever now thought to be of "obscure" or "unknown" origin.

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Clinical Studies

Hereditary Nephropathy, Deafness and Renal Foam Cells*

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THE possibility of an hereditary relationship between the structure and function of the ear and the kidney was noted early in this century [*1–4*]. However, this problem aroused little interest until Perkoff and his associates recently described a family with a high incidence of associated renal disease and deafness [*5,6*]. Since then the hereditary nature of the deafness and renal disease, the increased severity of the renal disease in males, and the occasional occurrence of ocular defects has been confirmed by many others [*7–18*].

This report describes a family with hereditary nephropathy and deafness, and reviews some of the unusual pathologic features associated with the syndrome. The family was called to our attention by the death of a young man with terminal uremia and deafness. Microscopic examination of the kidneys in this patient revealed a picture compatible with chronic glomerulonephritis. In addition, large numbers of foam cells were present in the kidneys. In an effort to determine the significance and incidence of renal foam cells in the two forms of renal disease that have been considered the most likely pathologic process in hereditary nephropathy, the records of 105 consecutive autopsy cases of chronic glomerulonephritis as well as 105 consecutive autopsy cases of pyelonephritis were reviewed. It is the purpose of this report not only to enlarge upon the present experience with hereditary nephropathy and deafness, but also to demonstrate that renal foam cells are not limited to cases of hereditary nephropathy.

CASE HISTORY

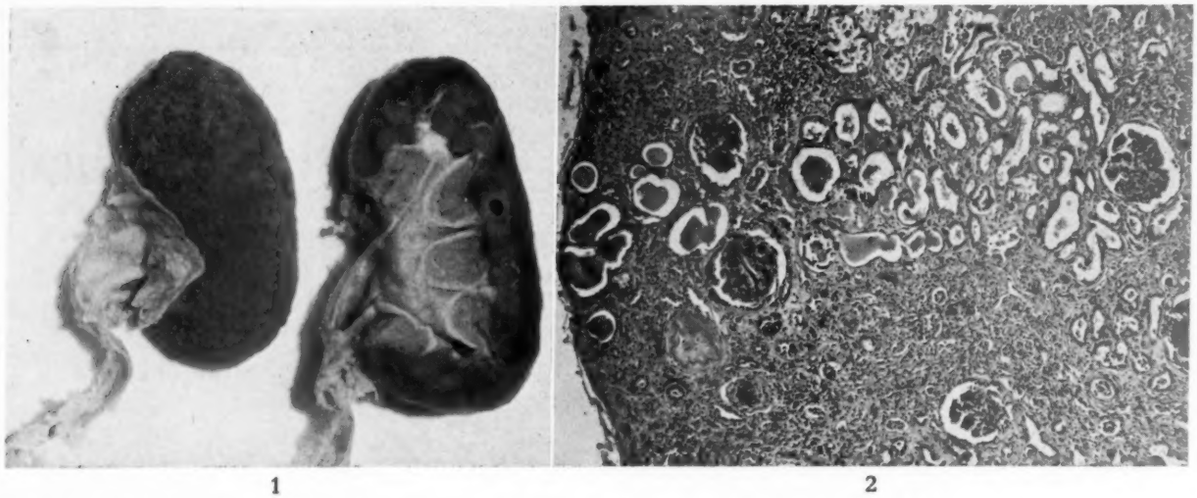
Thomas St. J., a twenty-four year old white married man with progressive uremia, was transferred to Duke Hospital on March 18, 1958, for consideration of hemodialysis. Except for a history of Rocky Mountain spotted fever at the age of eleven and an uncomplicated appendectomy at the age of thirteen, the patient had apparently been in excellent health until his present illness.

Four years prior to this admission, at the age of twenty, he was rejected for military service because of proteinuria. He denied any symptoms of renal disease, and remained asymptomatic except for slight decrease in hearing until approximately one year prior to admission. At that time he had an episode of malaise, low back pain and low grade fever. Despite therapy with antibiotics his symptoms recurred sporadically until six months prior to admission when he noted the onset of intermittent epistaxis, several episodes of gross hematuria, increasing malaise, easy fatigability and recurrent nausea. These symptoms gradually increased in frequency and intensity. Two weeks prior to admission an upper respiratory infection developed which was shortly followed by marked increase in lethargy, sudden onset of dependent edema and episodes of disorientation. Over the year prior to admission the patient's hearing had gradually decreased until he was moderately deaf.

Because of swelling of the face and edema of the

* From the Departments of Medicine and Pathology, Duke University Medical Center, Durham, North Carolina. This study was presented in parts at the annual meeting of the American Society of Human Genetics in Memphis, Tennessee, April 28, 1960, at the IV International Congress for Clinical Pathology in Madrid, Spain, June 15, 1960, and at the Annual Meeting of the American College of Physicians in Miami, Florida, May 12, 1961. This investigation was supported in part by research grant (8-3343H 1217) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, and grants from the American Heart Association and the North Carolina Heart Association. Manuscript received August 11, 1960.

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1 2

FIG. 1. Gross appearance of the kidneys showing the atrophic fine granular cortex. Original magnification × 1.2.

FIG. 2. Microscopic appearance of the kidney, showing the features of chronic glomerulonephritis. Hematoxylin and eosin stain, original magnification × 114.

legs, with a 20 pound weight gain, the patient was admitted to a local hospital. One week later he was transferred to Duke Hospital for consideration of the use of the artificial kidney. A preliminary review of the family history revealed a high incidence of renal disease and deafness. (A detailed family history follows the case history.)

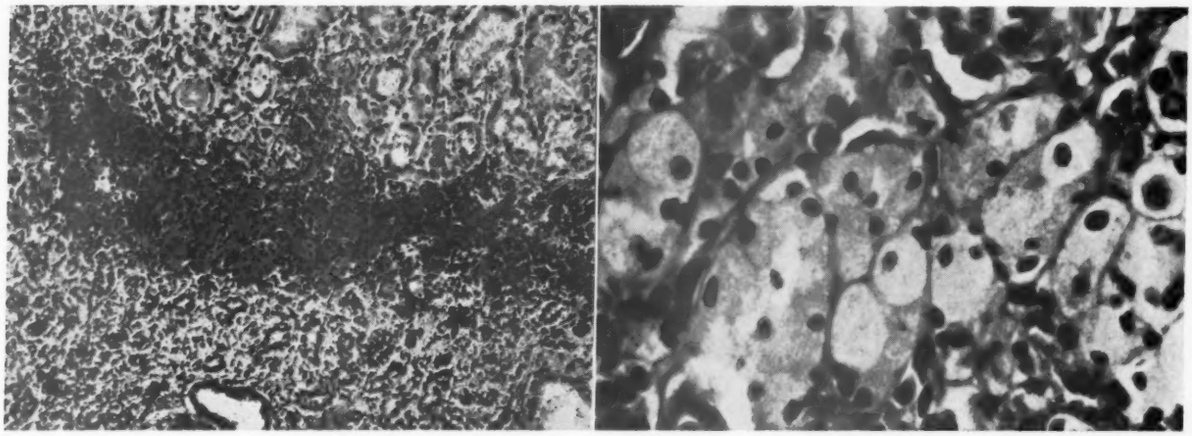
The physical examination on admission revealed a pulse of 88, respirations of 18, a blood pressure of 140/90 mm. Hg, and a temperature of 36.6°C. The patient was a well developed, pale, lethargic white man who appeared acutely and chronically ill. Edema of the face and ankles was prominent. There were multiple ecchymotic areas around the eyes and he was noted to have a uremic breath. Other positive physical findings included moderate bilateral deafness, arterial narrowing in the fundi, multiple dental caries, and a grade 2 precordial systolic murmur heard best along the left sternal border with minimal radiation into the neck. The results of the remainder of the physical and neurological examinations were normal.

The laboratory data on admission included a hemoglobin of 9.1 gm. per cent, hematocrit 25 per cent, reticulocyte count 4.4 per cent, white blood cell count 8,800 per cu. mm. with a normal differential smear. Urinalysis revealed a pH of 5, specific gravity of 1.011, 3-plus proteinuria and no glycosuria. The urinary sediment had 6 to 12 red blood cells, 5 to 20 white blood cells, and several granular casts per high power field of centrifuged specimen. The reaction to serological test for syphilis was negative. The stool guaiac test was negative. The erythrocyte sedimentation rate was 12 mm. in one hour (corrected). A lupus erythematosus preparation was negative. There was no phenolsulfonphthalein excretion in two hours. The patient was in marked metabolic acidosis, with hyperkalemia and azotemia. The fasting blood sugar, serum total protein and cholesterol were within normal limits. A chest roentgenogram revealed slight cardiac enlargement but was otherwise within normal limits. The electrocardiogram was essentially normal except for definite peaking of the T waves in leads V_2 through V_4.

Although it was clear that the patient had severe chronic nephritis, the possibility of reversing a suspected acute exacerbation of the disease led to the use of the twin coil artificial kidney. During the course of hospitalization the patient was hemodialyzed on two occasions, with marked reduction in both the biochemical and clinical signs of uremia. Eighteen days after admission he was discharged, to be followed up in the Outpatient Department.

Improvement was short-lived, and approximately one month after discharge the patient was readmitted to the hospital to be prepared for an operation to allow perfusion of an isolated ileal loop in an effort to provide long-term control of the azotemia and chronic electrolyte derangement. The physical examination revealed a blood pressure of 170/100 mm. Hg, increased lethargy, definite cardiomegaly and early signs of congestive heart failure. Laboratory investigation revealed more marked anemia and accentuation of the previous electrolyte abnormalities. Less than 100,000 Staphylococcus albus organisms were cultured from 1 ml. of urine.

Prior to surgery the patient was hemodialyzed for the third time, with temporary correction of his biochemical abnormalities and clinical state. A segment of the ileum was isolated and both ends of the isolated loop were exteriorized, allowing perfusion of the loop with selected electrolyte solutions. Due to difficulties in controlling fully the exchange of fluid and electrolytes across the wall of the ileal segment, adequate regulation of serum electrolytes was never



3 4

FIG. 3. Low power view of the foam cells arranged in clusters and rows in the scarred cortical tissue of the kidney. Oil Red O stain, original magnification × 196, with yellow filter.

FIG. 4. High power view of the foam cells, demonstrating the fine reticular structure of the cytoplasm. They appeared to be packed in spaces formerly occupied by tubules. On the left side of the photograph the original tubular basement membrane is well delineated and delicate. Hematoxylin and eosin stain, original magnification × 978.

obtained. The patient died in uremia approximately one month after the operation.

At autopsy gross examination revealed remarkably contracted and atrophic kidneys. (Fig. 1.) The left kidney weighed 40 gm., the right kidney 50 gm. The renal capsule was slightly thickened but stripped easily. The cortex was finely granular, pale gray-brown, with a few retention cysts and dark red hemorrhagic spots. The cut surface of the kidney revealed a cortex of 3 to 4 mm. thickness. A few yellow flecks were seen in the cortical area. These were later shown to represent clusters of foam cells. The corticomedullary junction was indistinct. The main renal arteries appeared to be normal, but the arcuate vessels were prominent. There was no evident chronic inflammatory change in the pelvis.

Other pertinent findings were related to chronic hypertension, renal insufficiency and their complications. These included hypertrophy of the heart (weight 510 gm.), fibrinous pericarditis, bilateral pulmonary edema, pulmonary hemorrhages, confluent bronchopneumonia, generalized anasarca, cerebral edema, hydrothorax, ascites and hyperplasia of the four parathyroid glands. The jejunoileostomy orifice was patent and the incision well healed. The isolated ileal loop was patent but showed mucosal edema.

Microscopic examination of the kidney disclosed a remarkable reduction in the number of glomeruli. (Fig. 2.) Many glomeruli had undergone complete hyalinization and were almost indistinguishable from the surrounding scars. All the remaining glomeruli had undergone various degrees of alteration. Clubbing and adhesions of the capillary tufts were seen in some, while proliferation of epithelial cells forming an atypical crescent were noted in others. Hyaline thrombosis and disruption of the capillaries associated with hemorrhage into Bowman's space were occasionally seen. The corresponding tubules were atrophic or unrecognizable. The well preserved tubules often were hypertrophied and dilated with large hyaline casts filling the lumens. The arteries were sclerotic.

Many large foam cells were seen within the scarred cortical area. (Figs. 3 and 4.) Frequently they were present in rows, as if occupying areas previously occupied by tubules. Many of the cells were packed into what appeared to be spaces lined by a normal or thickened tubular basement membrane. Other foam cells were scattered at random and were separated by young reticulum and connective tissue fibers which formed a part of the cortical scars.

The foam cells ranged between 50 and 80 μ in size, and stained brilliantly red with Oil Red O, indicating the presence of neutral fat. With hematoxylin and eosin stain of Zenker-formol-fixed tissue these cells were found to contain a light brown reticular structure. The reticular structures were slightly stained by the periodic acid-Schiff procedure and took a Luxol fast blue stain, indicating the presence of mucopolysaccharides and phospholipids, respectively. These structures were not acid-fast, nor were they stained with Alcian Blue, indicating the absence of acid mucopolysaccharides. Birefringent needle shaped crystals and a few crystals in the shape of Maltese crosses were noted when the frozen section was examined with polarized light. These crystals consisted of cholesterol and phosphatides. In addition to that seen in foam cells, small amounts of fat were also present in tubular casts, epithelial cells and connective tissue elements. Foam cells of similar morphologic characteristics were also seen in great numbers in the pulmonary alveoli, but in no other organs.

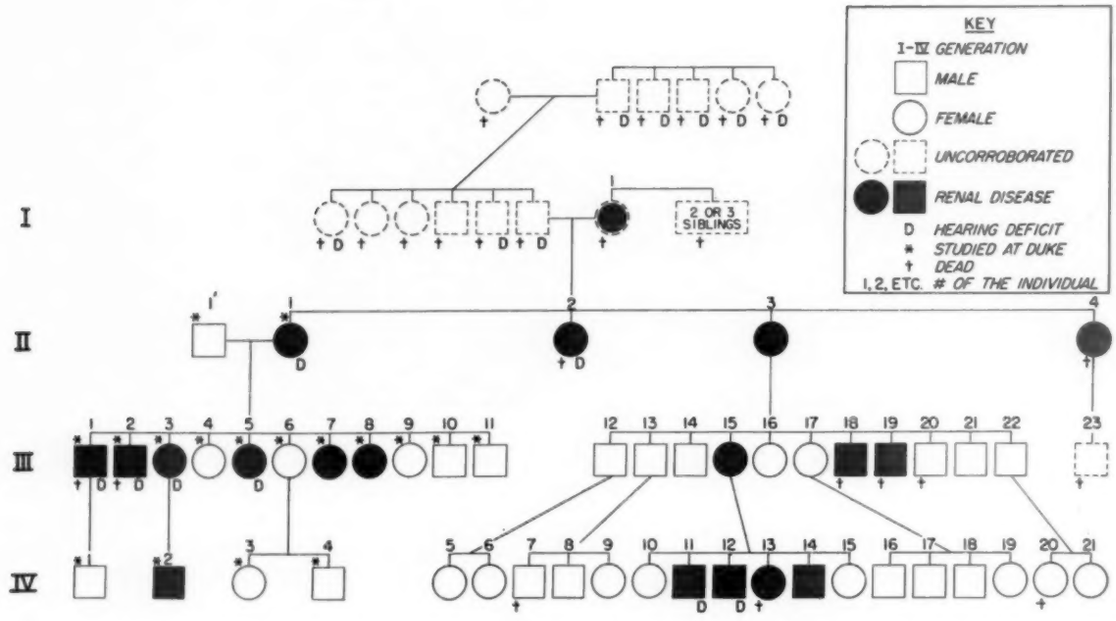


FIG. 5. Pedigree.

Examination of the middle and inner ear failed to disclose any significant changes. Detailed cytologic changes of the inner ear structures were difficult to evaluate because of decalcification artefacts. Step sections through the VII and VIII nuclei in the brain stem revealed only non-specific degenerative changes such as fatty infiltration and slight chromatolysis in some of the neurons. Microscopic examination of the other organs confirmed the gross diagnosis.

FAMILY STUDY

The high incidence of renal disease and deafness in the family history prompted a more extensive investigation of the patient's family. When direct examination of relatives was impossible, clinical information was obtained from hospitals and physicians who had cared for members of the family. The members studied at Duke Hospital are denoted by an asterisk on the pedigree. (Fig. 5.) Members indicated by solid symbols without an asterisk have been documented by correspondence with physicians or several reliable historians. The members indicated by dotted symbols are known only by uncorroborated reports from one member of the family. This family has also been the subject of a recent report by Chappell and Kelsey [*17*].

The examination consisted of a complete history, physical examination, hemoglobin, hematocrit, white blood cell count, differential count, urinalysis (including specific gravity, pH, protein, sugar and study of urinary sediment), antistreptolysin O titer, non-protein nitrogen, serum protein electrophoresis and audiometry. A person was considered to have renal disease if proteinuria exceeded 1 plus with the sulfosalicylic acid test, or if 1-plus proteinuria was accompanied by more than 5 red blood cells or 10 white blood cells per high power field of centrifuged urine.

Figure 5 gives a summary of the history of the family. The generation is indicated by Roman numerals and the individual members of each generation designated by Arabic numbers. III-1 is the propositus. There is no known consanguinity. The clinical status of the first two generations except for I-1 is not well known and therefore the outline is in dotted lines. Several members of generation IV who have no urinary abnormality are in childhood. It cannot be stated unequivocally that these children are free of disease, since it is conceivable that the renal disease will become manifest later. This seems unlikely, however, since the urinary abnormalities usually appear very early in life.

It is believed that I-1 is the source of the trait in later generations. Therefore, I-1 is considered to be the only member of the first generation, although she is thought to have had several siblings. I-1 died at the age of twenty-five with "dropsy" and is believed to have had renal disease. She was not deaf. She had four female

offspring. It is interesting to note that there is a high incidence of deafness among the relatives of the husband of I-1, but no renal disease.

II-4 died in uremia which was apparently precipitated by her only pregnancy. Her only child (III-23) died of an unknown cause in childhood.

II-3 has renal disease without deafness by history although she has not been studied. Two of her sons (III-18 and III-19) died of renal disease but without deafness. One daughter (III-15) with renal disease has three sons (IV-11, IV-12 and IV-14) who are afflicted. One of her daughters (IV-13) also had renal disease but died of septicemia.

II-2 died deaf and childless at the age of sixty-five with a history of chronic renal disease.

II-1 is the mother of the more completely studied portion of the family. She has both renal disease and complete nerve deafness. Her history is of further interest in that she had a severe exacerbation of renal disease during her sixth pregnancy but has had no trouble since then. Her husband (II-1′) gave a history of acute glomerulonephritis at the age of eighteen without sequelae. Examination now fails to reveal any evidence of renal disease or deafness.

Two sons (III-1 and III-2) have already died with both features of the trait. The only son (IV-1) of III-1 is normal at present. Two other sons (III-10 and III-11) are normal. Four daughters (III-3, III-5, III-7 and III-8) have renal disease and two of these have abnormal audiograms. III-3 gave a history of an exacerbation of her renal disease during her pregnancy. Her son (IV-2) now has renal disease without deafness. Three other daughters (III-4, III-6 and III-9) have no evidence of disease. Offspring of III-6 (IV-3 and IV-4) appear to be normal.

It is of further interest that three of the afflicted members of this family (II-1, III-1 and IV-2) have a clear-cut history of asthma. Four members of the family who have been studied had eosinophilia greater than 8 per cent on differential smear, but this had no correlation with the presence of renal disease, deafness or asthma.

Routine blood studies were within normal limits except in the patients who died. Serum electrophoresis has failed to further characterize those afflicted, except IV-2 who has a low gamma globulin level. Antistreptolysin titers were elevated in several members, but they were asymptomatic. Only two people (II-1 and III-8) with renal disease had an elevated titer. Examination of the urinary sediment with polarized light of several afflicted members of the family did not demonstrate birefringent fat bodies. Physical examinations failed to reveal other definite anomalies and there was no evidence of ocular defects.

TABLE 1
ANALYSIS OF 105 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS AND 105 PATIENTS WITH PYELONEPHRITIS

	Glomerulonephritis		Pyelonephritis	
	No.	%	No.	%
Patients with foam cells	9	8.5	6	5.7
Patients with family history available	96	91.4	95	90.4
Patients with foam cells and a family history of renal disease	5	55.5	1	16.7
Patients without foam cells but a family history of renal disease	19	21.8	4	4.4

FOAM CELLS IN OTHER CASES OF CHRONIC GLOMERULONEPHRITIS AND PYELONEPHRITIS

In order to establish the significance of the foam cells in the kidney in our cases, one of us (S. H.) reviewed the records of 105 consecutive autopsy cases of chronic glomerulonephritis as well as the same number of autopsy cases of pyelonephritis from the Duke Hospital autopsy files. The number of kidney sections reviewed varied from two to ten for each case. These included some special stains such as fat, periodic acid-Schiff, connective tissue stains and, less frequently, several others. At least two routine hematoxylin and eosin sections were scrutinized for the presence of foam cells. These large cells with pyknotic nuclei and foamy cytoplasm were found in the scarred renal cortex of patients with both diseases. Brief summaries of the clinical and pathologic features of all the patients with chronic glomerulonephritis and pyelonephritis who demonstrated renal foam cells are recorded subsequently.

Table 1 summarizes the pertinent features of the two groups of renal disease studied. Because of the small number of patients demonstrating

TABLE II
FURTHER ANALYSIS OF NINE PATIENTS WITH CHRONIC GLOMERULONEPHRITIS AND FOAM CELLS

	No.
Hereditary nephropathy with deafness	2
Hereditary nephropathy without deafness	1
Family history of renal disease	2
No family history of renal disease	4*

* Includes one patient with arabinosis.

renal foam cells and because of the necessity for a retrospective evaluation of the family histories from clinical records, the figures are not believed to be statistically significant. It is conceivable that a more extensive evaluation of patients with foam cells and a negative family history of renal disease might uncover such a history, but this has been impossible to do. The data are presented, however, to give an over-all picture of the distribution of renal foam cells in chronic glomerulonephritis and pyelonephritis.

In the group with glomerulonephritis, there were nine patients with renal foam cells. (Table II.) Two (the propositus and Case A) are believed to be members of families with hereditary nephropathy and associated deafness. One (Case B) is from a family now under study that has hereditary nephropathy without deafness. Two (Cases G and H) have clear-cut family histories of renal disease but the data are inadequate to label these families categorically as examples of hereditary nephropathy. Four (Cases C, D, E and F) came from families without a history of renal disease. The significance of the foam cells in one of these patients (Case C) is obscured by the fact that gum acacia is known to induce arabinosis with foam cell formation in human and animal kidneys [*19,20*].

In the group with pyelonephritis, there were six subjects with renal foam cells. Included in this group were patients with xanthogranulomatous pyelonephritis (Case J), de Toni-Fanconi syndrome with cystinosis (Case N) and Wegener's granulomatosis with renal abscess formation (Case M). There was a lower incidence of a family history of renal disease in this group as compared to those in the group with glomerulonephritis. This held true not only when all patients in the two groups were compared but also when only those with renal foam cells were considered.

CASE A (*Chronic Glomerulonephritis*). A twenty year old white man was admitted to Duke Hospital in August 1934 with the chief complaint of edema of the ankles for five months. He had had kidney trouble and many ear infections since nine years of age. His only brother also had renal disease but a sister did not. His father was living and well at the age of fifty-one. His mother was thirty-five when she died of influenza in 1918.

On physical examination he had marked impairment of hearing. Bilateral posterior cataracts were noted. He had 4 plus proteinuria but no azotemia. The clinical findings were consistent with subacute glomerulonephritis. One year later, on his second admission to this hospital, he died with uremia and hypertension. At autopsy the kidneys were contracted, weighing a total of 100 gm. Many yellow flecks and streaks were noticed in the finely granular cortex. Microscopic examination led to a diagnosis of chronic glomerulonephritis. Many characteristic foam cells were present in the scarred cortex. (Fig. 6A.) No statement was made concerning any changes in the eyes or ears.

Comment: The deafness, lenticular opacities, history of ear infections, family history of renal disease, and early death with glomerulonephritis are so typical of the syndrome under discussion that we believe this to be another case of hereditary nephropathy with deafness. Although a family study was not possible, this patient is not thought to be related to the pedigree in Figure 5.

CASE B (*Chronic Glomerulonephritis*). The patient was a seventeen year old white single boy who was first admitted to Duke Hospital in January 1959 with chronic renal disease. Proteinuria had been noted at six years of age. Over the ensuing years he was seen in several hospitals. Laboratory signs of renal disease gradually progressed until 1958 when azotemia developed. His course was slowly downhill despite supportive measures and he died in uremia at Duke Hospital in November 1959.

Review of the family history revealed that his mother has a history of persistent proteinuria and hematuria since the age of eight. One of his half brothers has chronic renal disease, whereas another half brother has no apparent renal abnormality. Both half brothers are offspring of the affected mother. A maternal grandmother has a normal urinalysis and a normal audiogram for her age. Neither the patient nor his mother had abnormal audiograms. An extensive evaluation of the family history failed to reveal any other evidence of renal disease.

Significant autopsy findings included extremely small granular kidneys, weighing a total of 78 gm. Microscopic examination demonstrated changes

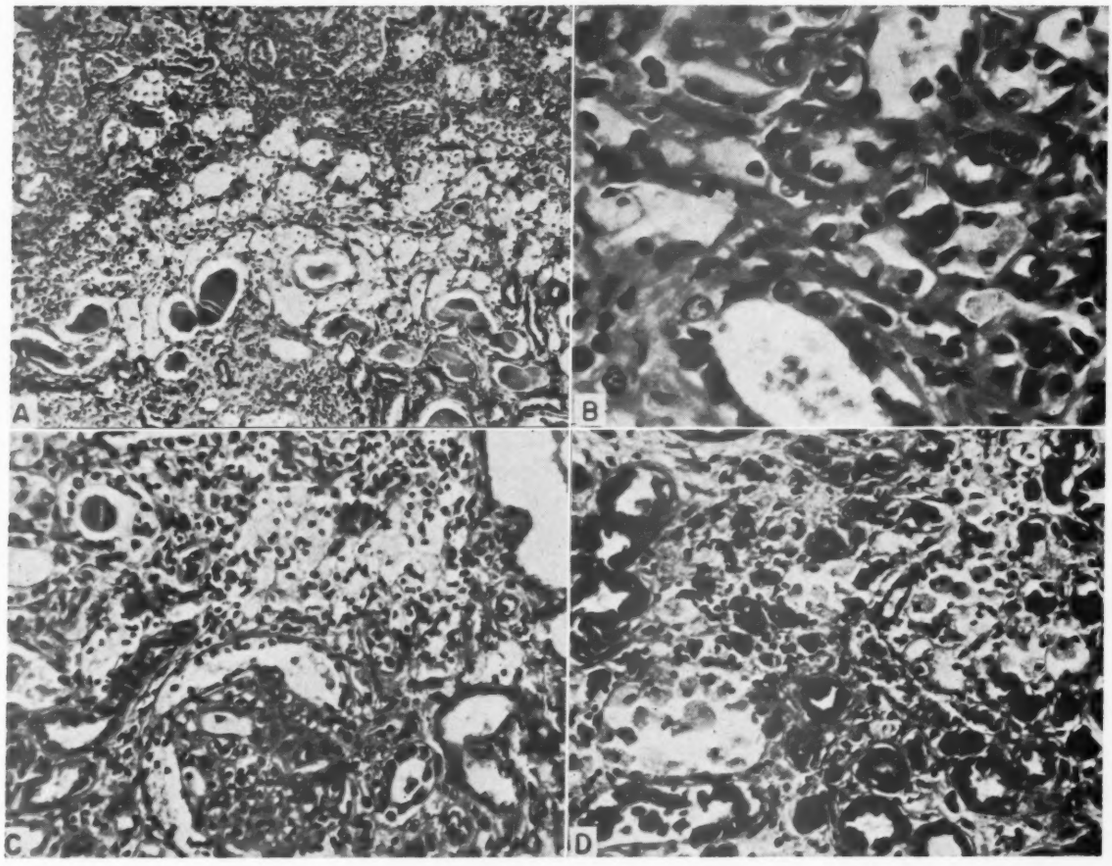


FIG. 6. Reduced to one-quarter of original magnification. A, Case A. Low power view of the characteristic foam cells. Compare with Figures 3 and 4. Hematoxylin and eosin stain, magnification × 196. B, Case B. Arrows denoting a few scattered foam cells. The kidneys are severely contracted, but the foam cells are rather sparse. Hematoyxlin and eosin stain, magnification × 978. C, Case C. Foam cells are present both in the interstitium and the glomerulus. Hematoxylin and eosin stain, magnification × 391. D, Case D. Some foam cells line the tubular basement membrane as if transformed from the tubular epithelium. Some foam cells are seen in the tubular lumen. Hematoxylin and eosin stain, magnification × 391.

compatible with chronic glomerulonephritis. There were a few foam cells scattered throughout the cortex. (Fig. 6B.)

Comment: This would appear to be an example of hereditary nephropathy without deafness. That all three family members have acquired rather than hereditary renal disease remains a possibility because of the presence of the disease in only two generations and the absence of fhe disease in three generations preceding the mother. However, the mother's thirty-two year history of marked abnormalities of the urine without azotemia or symptoms, the presence of renal disease in half brothers, and the early death of the patient certainly is in favor of this being hereditary nephropathy. The affliction in half brothers would fortuitously label the trait as one transmitted by the mother.

CASE C (*Chronic Glomerulonephritis with Arabinosis*). An eighteen year old white boy was admitted to Duke Hospital in July 1945 with progressive edema for one month. The patient had sustained a puncture wound of his left great toe one month prior to admission, for which he had received tetanus antitoxin. One week following the injection puffiness of the eyes in the morning, vague abdominal pain, frequent loose stools and progressive edema developed. There was no family history of renal disease or deafness. Physical examination revealed a normal blood pressure but peripheral edema. Laboratory examinations disclosed transient azotemia, persistent proteinuria, hypoalbuminemia and hypercholesterolemia. During hospitalization his condition deteriorated. He accumulated more fluid and was treated with intravenously administered gum acacia without benefit. He had a six months hospitalization with gradual stabilization, but evidence of severe renal damage persisted. Six months after his discharge he was readmitted with terminal uremia. He died one month later.

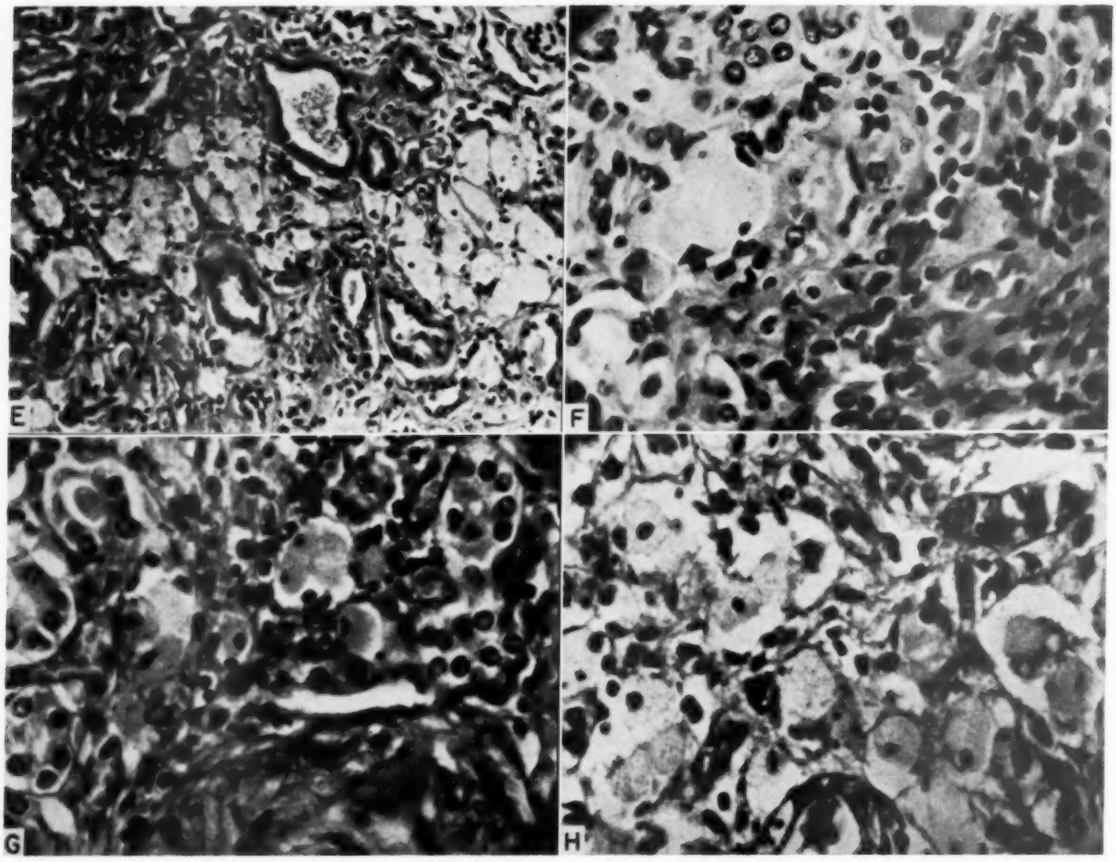


FIG. 7. Reduced to one-quarter of original magnification. E, Case E. Large clusters of foam cells can be seen in the center of the section. Hematoxylin and eosin stain, magnification × 391. F, Case F. A few large foam cells such as those marked by the arrow were seen. Hematoxylin and eosin stain, magnification × 978. G, Case G. A small group of foam cells can be seen in the center of the section. Hematoxylin and eosin stain, magnification × 978. H, Case H. A large number of foam cells are seen scattered throughout the section. Hematoxylin and eosin stain, magnification × 978.

At autopsy gross examination revealed that the kidneys were large and swollen, weighing 180 and 190 gm., respectively. The cortex was smooth and speckled with ochre-colored spots. Microscopically, some glomeruli showed hyaline thickening of the capillary tufts, others scarring. Many foam cells were prominently seen in the fibrotic cortical area and occasionally in the glomerular capillaries. (Fig. 6C.) Similar cells were also seen in the lungs, spleen, liver and lymph nodes. Some of the foam cells were demonstrated to contain fat, others did not. Morphologically, they resembled the foam cells of our patient. However, after extensive studies performed at that time, the material in the foam cells was concluded to be gum acacia without all the staining characteristics seen in the propositus of our family.

Comment: The foam cells seen in the kidney were indistinguishable from those seen in many other organs. The patient did not present any family history of nephritis or deafness. Clinically he had the nephrotic syndrome which has not been reported in other cases of hereditary nephropathy with deafness. The foam cells were thought to contain gum acacia.

CASE D (*Chronic Glomerulonephritis*). A twenty-eight year old white man was incidentally noted to have proteinuria during a preinduction physical examination. He was therefore rejected for military service. In April 1944, he was admitted to Duke Hospital for the first time. The family history was non-contributory. Physical examination did not reveal any abnormalities and there was no evidence of deafness or visual disturbances. Urinalysis revealed persistent 1 to 3 plus proteinuria, red blood cells, white blood cells and casts in the urinary sediment. Four years later this patient was readmitted with progressive uremia. Supportive therapy was of little help and two months after discharge he was readmitted for the third time. He died in uremia shortly after admission.

At autopsy gross examination revealed markedly contracted kidneys weighing 90 and 80 gm., respectively. The microscopic features were those of chronic

glomerulonephritis. Characteristic foam cells were seen in the fibrotic cortical area, but they were few in number. (Fig. 6D.)

Comment: There was no family history of renal disease, but information available referred only to the health of the patient's siblings and his parents. A few foam cells were noted in the kidney, although the patient and his immediate family had no other stigmata of the syndrome of hereditary nephropathy and deafness.

CASE E (*Chronic Glomerulonephritis*). The patient was a twenty-two year old married Negro woman who was admitted to Duke Hospital in December 1953. Four years prior to admission she had had a five day episode of gross hematuria. She did well thereafter until five months prior to admission when severe headaches developed during her fifth month of pregnancy. Upon admission to the local hospital she was noted to have marked hypertension and poor renal function. A hysterotomy and sterilization procedure were performed. She was asymptomatic until one week prior to admission when swelling of the left orbit and headache developed. On examination she was noted to be hypertensive, with evidence of early heart failure. Laboratory examination revealed a normochromic normocytic anemia, proteinuria, hematuria, pyuria and azotemia. She died in uremia six days after admission.

The patient had denied a family history of renal disease.

At autopsy both kidneys were contracted and small. Yellow streaks were noted throughout the cortical areas. Microscopic examination revealed clusters of typical foam cells in the scarred cortex. (Fig. 7E.)

Comment: A family history including two generations failed to disclose any other cases of renal disease, yet the kidneys contained typical foam cells.

CASE F (*Chronic Glomerulonephritis*). The patient was a twenty-six year old white man with a history of hematuria at age six, persistent proteinuria at age thirteen and hypertension at age twenty-four. In April 1951 he was admitted to Duke Hospital where he was noted to have hypertension, hypertensive retinopathy, cardiomegaly, proteinuria and azotemia. The patient died in uremia during his second hospitalization in June 1951. The patient gave no family history of renal disease.

Grossly the kidneys were small and scarred. Microscopically, foam cells were noted in the atrophic cortex. (Fig. 7F.)

Comment: Foam cells were present in the kidneys, although there was no family history of renal disease.

CASE G (*Chronic Glomerulonephritis*). The patient was a thirty-two year old white married man who was noted to have asymptomatic proteinuria six years prior to his first admission to Duke Hospital in January 1958. One month prior to admission severe headaches developed with gradually progressive loss of vision. Upon admission marked hypertension with severe retinopathy, cardiomegaly, congestive heart failure, proteinuria, hematuria and azotemia were noted.

A review of the family history disclosed that his brother had been rejected for military service because of proteinuria and that persistent 4 plus proteinuria had since developed.

The patient was discharged and instructed to follow a regimen consisting of the rice diet and antihypertensive drugs, which failed to halt his steady downhill course. Six months later, during his second hospitalization, he died in uremia.

At autopsy the kidneys were small and contracted, with a granular surface. Small yellow dots and streaks were noted in the cortical areas. Microscopic examination disclosed scattered clusters of foam cells in the cortex. (Fig. 7G.)

Comment: This patient's brother has proteinuria and has been carefully studied in two other hospitals. There is no other evidence of familial nephropathy. The foam cells are indistinguishable from those seen in other cases of hereditary nephropathy.

CASE H (*Chronic Glomerulonephritis*). The patient was a nineteen year old white single girl who had a trace of protein in her urine four years prior to admission, hypertension three years prior to admission and severe hypertensive retinopathy three months prior to admission. Despite vigorous dietary therapy she died during her first admission to Duke Hospital in June 1950.

Her family history was of interest in that both parents had hypertension and were living, and one grandmother had Bright's disease. There was no family history of deafness.

Gross examination of the small granular kidneys revealed small yellow flecks throughout the thin cortex. Microscopic examination of the kidneys demonstrated clumps of foam cells in the cortical areas. (Fig. 7H.)

Comment: This patient had a family history of renal disease but the information is inadequate to consider this an example of hereditary nephropathy. The clumps of foam cells were discernible both grossly and microscopically.

CASE I (*Chronic Pyelonephritis*). This four year old white girl was first admitted to Duke Hospital in 1956 with a two year history of persistent infection of the

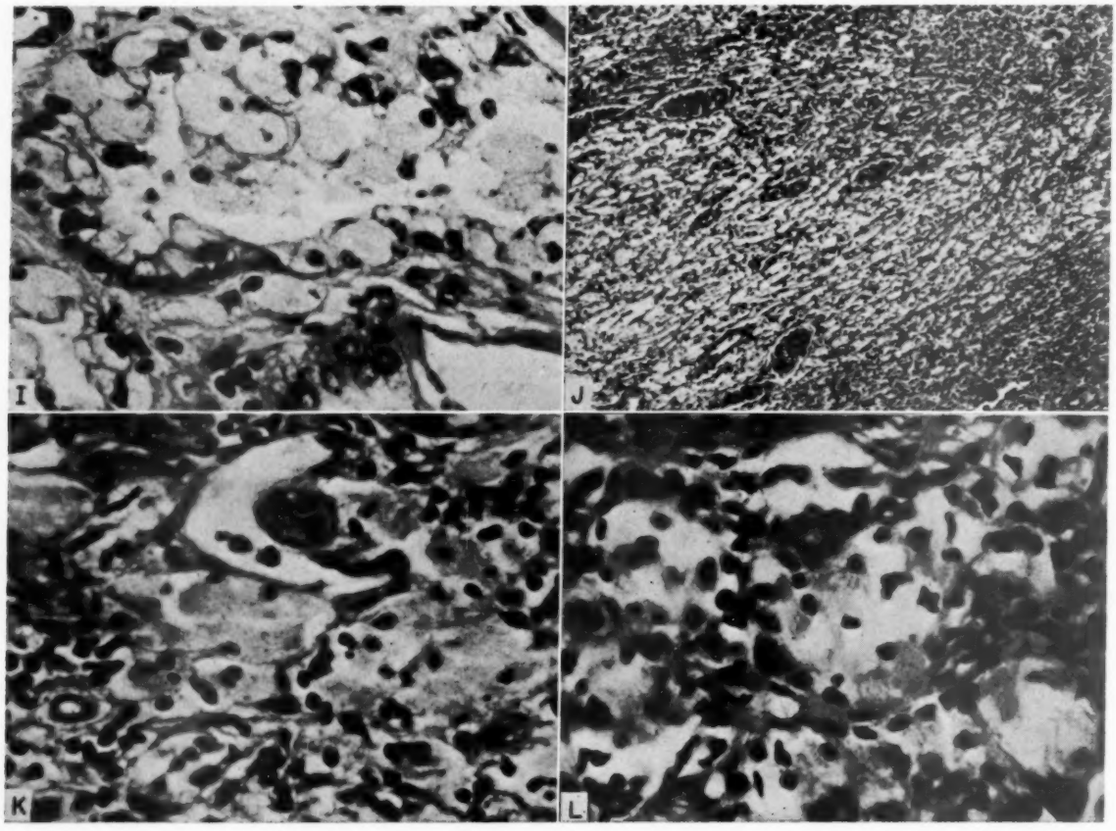


FIG. 8. Reduced to one-quarter of original magnification. I, Case I. Foam cells are apparently lining the tubular space suggesting that they originated from tubular epithelium. Notice that similar cells are also present in the interstitium. Hematoxylin and eosin stain, magnification × 829. J, Case J. Xanthogranulomatous lesions are present in the renal pyramid. There is a great deal of chronic inflammatory infiltration and a large number of foamy macrophages surrounding an abscess. Hematoxylin and eosin stain, magnification × 175. K, Case K. A few foam cells can be seen filling the interstitial spaces or tubules. Hematoxylin and eosin stain, magnification × 829. L, Case L. Foam cells can be seen in the tubules. Hematoxylin and eosin stain, magnification × 829.

urinary tract despite antibiotic therapy. Physical examination revealed no abnormalities but laboratory studies disclosed pyuria and bacilluria. Urologic studies revealed ureteral dilatation but no obstruction. There was mild azotemia and a slight elevation of the alpha two fraction on serum electrophoresis.

A review of the family history revealed that a maternal aunt died of Bright's disease at the age of four and another maternal aunt, as well as a first cousin, had had Bright's disease. Further follow-up of the family history failed to confirm a pattern of hereditary nephropathy.

Despite vigorous therapy, the patient died of renal failure at the age of six. Postmortem examination revealed bilateral ureteral dilatation without obstruction, and atrophic kidneys containing yellow streaks within the cortical scars. Microscopic examination revealed marked destruction of renal tissue with large foci of mononuclear and polymorphonuclear cells. The glomeruli showed not only hyalinization but also occasional necrosis and clubbing. Collections of foam cells were noted in the renal tubules (Fig. 8I.)

Comment: In view of the family history, it was initially suspected that this child might have had hereditary nephropathy. Further study of the family, however, failed to confirm this observation. We now believe that this patient had chronic pyelonephritis of unknown etiology and had renal foam cells on this basis.

CASE J (*Xanthogranulomatous Pyelonephritis*). The patient was a forty-nine year old Negro man who died of carcinoma of the bladder during his sixth admission to Duke Hospital in 1959. Despite a transurethral resection of a tumor on the bladder two years previously, he had required several operations to prevent ureteral obstruction. Eventually he required bilateral cutaneous ureterostomies. The patient was admitted for the last time with abdominal pain. He had no family history of renal disease.

Physical examination revealed a cachectic Negro man with extensive lymphadenopathy and signs of intestinal obstruction secondary to complete obstruc-

tion of the rectum by a large tumor. Despite an ileotransverse colostomy and drainage of a pelvic abscess the patient died three weeks after admission.

At autopsy the abdomen and pelvis were filled with adenocarcinoma. Both kidneys were almost completely filled with tumor implants and multiple abscesses containing greenish yellow pus. The ureters were dilated and thickened. Microscopic examination of the kidneys confirmed the presence of large abscesses and masses of necrotic tumor. There were large nests of foamy mononuclear cells in the renal pyramids surrounding the abscesses. (Fig. 8J.) Gram-negative rods were easily demonstrated.

Comment: This case is a striking example of xanthogranulomatous pyelonephritis with associated ureteral obstruction. The foam cells are similar to those reported in other such cases [*21,22*].

Case k (*Chronic Pyelonephritis*). The patient was a thirty-six year old white married woman who noted the onset of recurrent episodes of dysuria, back pain, fever and cloudy urine at the age of fifteen. She was first admitted to Duke Hospital at the age of thirty-four because of recurrent headaches. At that time she was noted to have hypertension with azotemia. Over the ensuing two years she was readmitted on five occasions for evaluation of the effect of the rice diet on her disease.

She was admitted for the seventh and last time in 1947 because of marked uremia. Physical examination revealed all the stigmata of terminal hypertensive vascular disease, including congestive heart failure. She died in uremia two weeks after admission. There was no history of renal disease in the family.

Postmortem examination of the kidneys revealed marked contraction and scarring. Microscopically there was marked disruption of the parenchyma with fibrous scars which were infiltrated with large numbers of lymphocytes and plasma cells. Scattered throughout these scarred areas were small collections of foam cells. (Fig. 8K.)

Comment: The history and the findings at pathologic examination were considered to be most compatible with chronic pyelonephritis. This patient with pyelonephritis had typical renal foam cells without a family history of renal disease.

Case l (*Chronic Pyelonephritis*). The patient was a thirty-one year old white married woman who died of chronic renal insufficiency in St. Luke's Hospital, Bluefield, West Virginia, in May 1949. At the age of sixteen, during her first pregnancy, renal complications developed which recurred with each of six succeeding pregnancies. Several years prior to her death recurrent edema and increasing fatigability developed. One month prior to admission refractory edema and dyspnea developed. A family history was not available.

On admission she was noted to be chronically ill in congestive heart failure. Laboratory studies revealed proteinuria, pyuria, anemia and azotemia. She gradually became more uremic and died two months after admission.

At postmortem examination the kidneys were atrophic and granular. On microscopic examination there was marked fibrosis with destruction of both glomeruli and tubules. The renal pelvis showed the typical changes of pyelonephritis. Small groups of foam cells were seen scattered throughout the cortical scars. (Fig. 8L.)

Comment: Pathologically this was a case of chronic pyelonephritis with renal foam cells. Unfortunately a family history was not available.

Case m (*Wegener's Granulomatosis with Renal Abscesses*). This fifty-seven year old white married man was admitted to Duke Hospital in 1948 with an illness of six weeks' duration. Initially he noted the onset of difficulty in hearing, later he was noted to have a stone in the left kidney, with pyuria. A large stone had been removed twenty-eight years previously, with subsequent asymptomatic pyuria. No family history was available.

Despite antibiotic therapy for several weeks prior to admission, the pyuria persisted. One week prior to admission arthralgias and weakness developed which necessitated complete bed rest. At this time he also noted the onset of a painful ulcer on his soft palate.

Physical examination revealed a poorly nourished, chronically ill white man with normal vital signs. There was moderate cardiomegaly and a painful, palpable left kidney, as well as the ulcer on the soft palate. Laboratory examination revealed a normochromic normocytic anemia, proteinuria, pyuria, azotemia, a large calculus in the left kidney with hydronephrosis, and an essentially normal appearing right kidney. Biopsy of the palatal ulcer revealed a non-specific granulomatous lesion. Chest roentgenograms revealed densities in both lung fields.

Ten days after admission pulmonary edema developed and the patient died. Postmortem examination revealed necrotizing granulomatous lesions involving the lungs, spleen and perinephric areas. In the lung the granulomatous lesions involved the pulmonary vessels, with associated infarction of parenchymal tissue. A large staghorn calculus was noted in the left kidney. Both kidneys demonstrated microscopic changes compatible with the diagnosis of chronic pyelonephritis. There were large abscesses throughout the parenchyma of both kidneys. Large numbers of foam cells lined the walls of these abscesses. (Fig. 9M.)

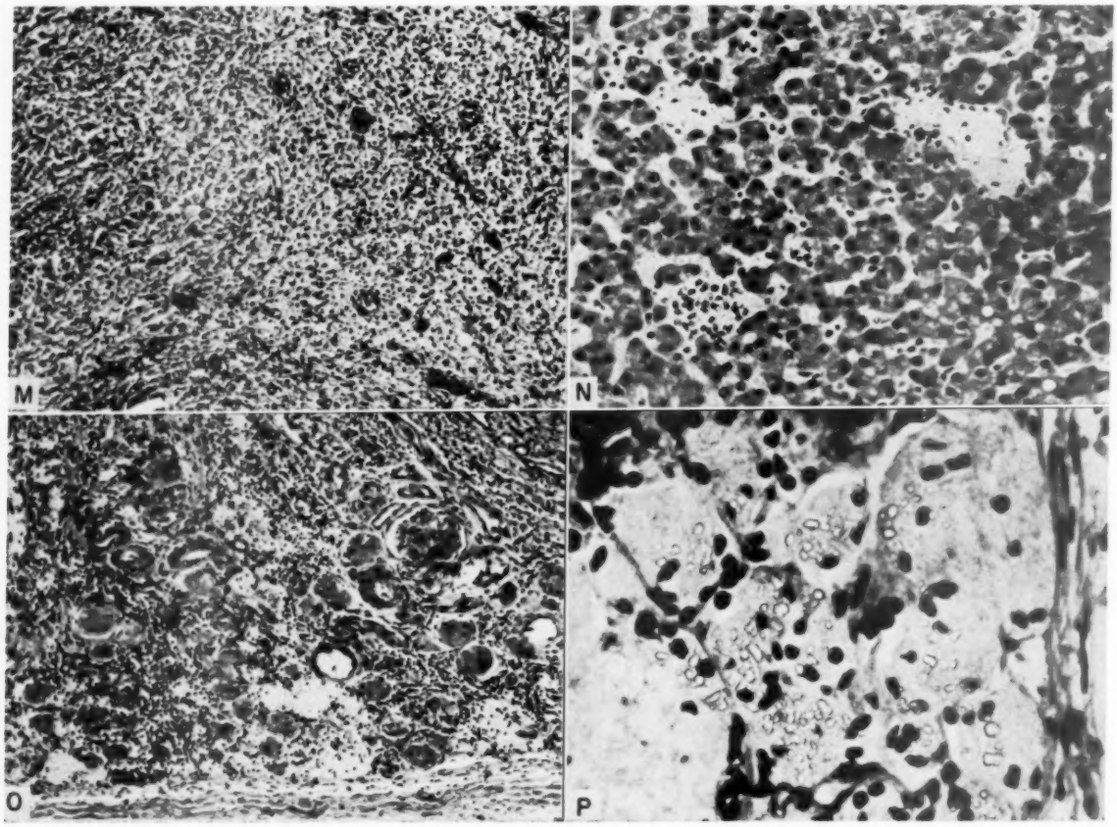


FIG. 9. Reduced to one-quarter of original magnification. M, Case M. Massive infiltration of foamy macrophages and chronic inflammatory cells is noted near the abscess in the renal pyramid of a patient with Wegener's granulomatosis. Hematoxylin and eosin stain, magnification × 175. N, Case N. There are focal collections of large vacuolated cells in the liver of this patient with the de Toni-Fanconi syndrome. There is some polymorphonuclear infiltration, but the liver cells appear normal. Hematoxylin and eosin stain, magnification × 175. O, Case N. Atrophy of the renal cortex, scarring of the glomeruli, loss of renal tubules, infiltration of lymphocytes, and the presence of many large clear vacuolated mononuclear cells are striking. Hematoxylin and eosin stain, magnification × 349. P, Case N. This is a high power view of the large vacuolated clear mononuclear cells seen in Figure O. The crystals are believed to be cystine. Hematoxylin and eosin stain, magnification × 928.

Staph. aureus organisms were cultured from the abscesses.

Comment: This patient had the stigmata of Wegener's granulomatosis. To our knowledge renal foam cells have not been seen in uncomplicated cases of Wegener's granulomatosis. However, renal foam cells have been noted in staphylococcal abscesses in the kidney [*23*]. Thus the foam cells are probably related to the staphylococcal infection rather than to the Wegener's granulomatosis.

CASE N (*de Toni-Fanconi Syndrome with Cystinosis and Pyelonephritis*). The patient was a three year old white boy who was referred to Duke Hospital in 1957 with the diagnosis of de Toni-Fanconi syndrome. Because of poor growth, polyuria, polydipsia and vomiting, he was hospitalized at eleven months of age. Further study revealed rickets, azotemia, an elevated alkaline phosphatase level and hypophosphatemia. Following this he continued to show abnormally slow growth and progressive azotemia.

Upon admission to Duke Hospital he was noted to be small but well proportioned. Laboratory investigation revealed azotemia, metabolic acidosis, proteinuria, hyposthenuria and osteoporosis. The family history was non-contributory.

Despite vigorous treatment the patient died approximately one year later. Postmortem examination revealed small granular kidneys with indistinct corticomedullary boundaries. On microscopic examination of the kidneys there was marked interstitial fibrosis and lymphocytic infiltration as well as many areas containing small clusters and nests of clear cells which initially appeared quite similar to the foam cells under discussion in this paper. However, the foam cells in this case were negative to periodic acid-Schiff stain and did not contain neutral fat. Similar cells

were also seen in the liver and reticuloendothelial system of this patient. In addition, distinct crystals were present in the clear cells seen in the kidney. (Figs. 9N, 9O and 9P.) Although there were calcium deposits throughout the kidneys these crystals did not react with von Kossa calcium stain.

Comment: In view of the clinical picture and autopsy findings, we believe this is a case of the de Toni-Fanconi syndrome with cystinosis. The crystals noted in the clear cells seen in the kidney are quite similar to cystine crystals reported in other such cases. Although the cells in this case appeared similar to the foam cells seen in our other cases they differed in containing crystals; they did not contain neutral fat whereas renal foam cells in our cases did; and these cells were seen throughout the reticuloendothelial system, which was not true in our patients with renal foam cells, other than the patient with arabinosis. Similar cells have been reported in another patient with this syndrome [*24*].

COMMENTS

This is a report of the thirteenth family with the syndrome of hereditary nephropathy and deafness [*1–18*]. Table III reviews the literature and includes the renal pathologic process observed at autopsy or suspected from the history. In addition there are allusions to at least five families that have not been reported on [*14,16*]. Three other families are currently being studied by the Department of Pediatrics at Duke Hospital [*25*]. Thus, at least twenty-one families with the syndrome have been observed, leading one to suspect that this is a more common entity than originally supposed. Guthrie [*2*] reported the first family as an example of hereditary hematuria in 1902. The same family was studied by Kendall and Hertz [*2*], Hurst [*3*] and finally Alport [*4*] who emphasized for the first time that there was a high incidence of deafness. The subject attracted little interest until 1951 when Perkoff et al. [*5*] described a large family with renal disease and deafness. Since then families have been described in Italy, Israel, Canada and France, as well as the United States.

The syndrome is characterized by a high incidence of renal disease and nerve deafness appearing in several generations. Ocular defects have been noted in several families. An increase in ear infection has also been noted. Perkoff et al. [*5,6*] suggested that the trait is a partially sex-linked dominant. Graham, however, has

TABLE III
HEREDITARY RENAL DISEASE WITH DEAFNESS
REVIEW OF FAMILY STUDIES

Author and Year	Type of Renal Disease
Guthrie [*1*] 1902	Unknown
Kendall, Hertz [*2*] 1912*	Unknown
Hurst [*3*] 1923*	Unknown
Alport [*4*] 1927*	Unknown
Perkoff et al. [*5,6*] 1951	Pyelonephritis and/or glomerulonephritis
Sohar [*7,8*] 1954	Unknown
Reyersbach, Butler [*9,10*] 1954	Glomerulonephritis
Poli [*11*] 1955	Glomerulonephritis
Sturtz, Burke [*12*] 1956	Unknown
Hamburger et al. [*13*] 1956	Unknown
Goldbloom et al. [*14*] 1957	Pyelonephritis
Robin, Gardner [*15*] 1957	Pyelonephritis
Sturtz, Burke [*16*] 1958	Unknown
Chappell, Kelsey (Family 1) [*17*] 1960	Glomerulonephritis
Chappell, Kelsey (Family 2) [*17*] 1960	Glomerulonephritis
Whalen et al. (present series)†	Glomerulonephritis
Shaw and Glover [*18*] 1960	Pyelonephritis

NOTE: Plus eight families via personal communication [*14,16,25*].
* Same family described by Guthrie [*1*].
† Same as Family 2 reported on by Chappell and Kelsey [*17*].

reanalyzed the Utah kindred reported by Perkoff et al. and suggested that the trait is a sex-influenced dominant trait, rather than a partially sex-linked dominant one [*26*].

The nephropathy and deafness may occur singly but more commonly they are associated. The deafness may not be complete, and some members who have no gross hearing deficit have abnormal audiograms. Males are much more seriously afflicted and there are few reports of an affected male living past the age of thirty. On the other hand, females who are afflicted usually have a normal life span. This is not universally so, however, and some previous family studies list afflicted females who died in youth. In our family three females (I-1, II-4 and IV-13) died with renal disease at a young age. Pregnancy often seems to accentuate the signs of renal disease.

Our family is undoubtedly another example of this syndrome. The kindred is too small to characterize further the means of transmission of the trait, but either the partially sex-linked dominant or the sex-influenced dominant hypothesis would be applicable. All the affected males have died in the second or third decade of life. One male offspring (IV-1) of one of the deceased males (III-1) is apparently normal. Two females have renal disease and abnormal audiograms without clinically overt hearing loss. None of the members who were studied had a hearing deficit without renal disease. In three females (II-1, II-4, and III-3) a severe

exacerbation of renal disease was associated with pregnancy.

There is a wide variation in the urinary findings among afflicted members and at different times in the same patient. The urinary findings may range from 4 plus protein with red cells, white cells and casts to a trace of protein with almost a normal number of formed elements. Infection of the upper respiratory tract, infections with beta hemolytic streptococci [*15*] and pregnancy seem to accentuate the urinary abnormalities. Several members of our family have had proteinuria reported as 4 plus yet now have a trace to 1 plus. Pyuria and signs of pyelonephritis have been prominent features in some families while hematuria and signs of glomerulonephritis have been the outstanding features in others, as in our family.

Despite the similarity of clinical course and genetic pattern in all families studied, earlier pathologic reports suggested that the basic renal lesion in some families was glomerulonephritis [*9,10*] while in others it was pyelonephritis [*5,6*]. Perkoff et al. initially believed their family had pyelonephritis but in a followup report [*6*] point out that examination of biopsy material and autopsy specimens reveals that their family has many of the features of chronic glomerulonephritis. These authors suggest that the pathologic picture, especially with respect to the presence of foam cells, is atypical both for classic glomerulonephritis and pyelonephritis.

The benign findings on renal biopsy in childhood [*10*] despite markedly abnormal urinary findings, as compared to the advanced changes in the adult, suggest that there is a sequence of changes and that the pathological picture observed is dependent upon the age and severity of the process. Pyelonephritis, which has been frequently reported, is probably superimposed on a more basic lesion that closely resembles glomerulonephritis. The family reported in this paper would fall in the glomerulonephritis-like group without evidence of pyelonephritis.

Renal foam cells have been noted in three families with hereditary nephropathy and deafness [*5,10,14*] and in one family with hereditary nephropathy alone [*27*]. In addition, our review of the pathologic material from the first family in the report by Chappell and Kelsey [*17*] revealed that both members of this family who came to necropsy had glomerulonephritis, and one exhibited renal foam cells.

The presence of fat in the epithelial and connective tissue cells or fibers of the kidney is a common finding in a variety of renal lesions such as chronic glomerulonephritis, arteriolonephrosclerosis and pyelonephritis; but foam cells are not thought to be present in these diseases. These observations have led to conjecture as to the specificity of renal foam cells in hereditary nephropathy.

In "lipoid nephrosis," cortical adenomas and in adenocarcinoma of the kidney the epithelial cells may alter their appearance to such a degree that they are indistinguishable from the foam cells seen in our cases. Large numbers of typical foam cells have been described in patients with severe pyelonephritis associated with pyonephrosis [*21,22*] and in patients with extensive staphylococcal infections of the kidney [*23*]. Foam cells of endothelial origin have recently been described in kidneys of cirrhotic patients [*28*]. Endothelial foam cells have also been seen in the kidneys of diabetic patients. Although foam cells are present in many organs of patients with angiokeratoma diffusum universale (Fabry's disease), there are no reports of renal foam cells in this disorder. In a case of cystinosis, King and Lochridge [*24*] described cells similar to the foam cells seen in our cases.

Our analysis of a series of cases of chronic glomerulonephritis and pyelonephritis indicates that renal foam cells are not pathognomonic of hereditary nephropathy. Renal foam cells were found not only in patients with hereditary nephropathy but also in patients with glomerulonephritis without a family history of renal disease, xanthogranulomatous pyelonephritis, Wegener's granulomatosis with renal abscesses, and glomerulonephritis with arabinosis. One patient with the de Toni-Fanconi syndrome and cystinosis had clear cells in the kidney which could easily be mistaken for the renal foam cells under discussion in this paper.

However, five of nine patients with chronic glomerulonephritis with renal foam cells did have a family history of renal disease and three of these probably had hereditary nephropathy. This suggests that the discovery of foam cells in the kidneys of a patient with chronic glomerulonephritis should lead to a more vigorous search for a family history of renal disease.

The nature of the foam cells is difficult to determine, since we cannot be certain whether they are of mesenchymal or epithelial origin. The foam cells in our cases often appear to be packed into tubules and to be lining tubular basement

membranes, suggesting an epithelial origin. In other areas they appear singly scattered about the cortex, suggesting that they are macrophages. Castleman [*10*] believes that these cells are phagocytes, and Barrie [*21*] believed that the foam cells seen in xanthogranulomatous pyelonephritis originated from fibrocytes. Histologically and cytochemically the foam cells seen in hereditary nephropathy do not appear different from the foamy macrophages commonly seen in the atheroma of vessels, lipid pneumonia, silicosis and many other conditions. Thus the origin of these cells remains debatable.

Studies thus far have failed to elucidate the nature of the defect in these families. Goldbloom et al. [*14*] have suggested two hypotheses: (1) The disease may be due to a genetic effect exerted at a specific stage of embryologic development, so that renal, auditory and ocular structures are affected to varying degrees, or, (2) there may be an inherited enzymatic defect which allows the production of a substance that induces damage in several organ systems. It is conceivable that an abnormal metabolite or excess of a normal metabolite is the stimulus for formation of the renal foam cells seen in hereditary nephropathy and other forms of renal disease.

Serum electrophoresis and study of lymphatic drainage of the intestine [*6*], as well as routine studies, have failed to suggest a profitable approach to the problem.

SUMMARY

A family with hereditary nephropathy and deafness is described. Postmortem examination of one member of the family revealed changes compatible with chronic glomerulonephritis. Large numbers of foam cells were noted in the cortex of the kidneys. The staining characteristics of these cells suggest that they contain neutral fat, mucopolysaccharides, phospholipids, cholesterol and phosphatides.

Foam cells may be seen in a variety of renal lesions. A review of the records of 105 consecutive autopsy cases of chronic glomerulonephritis led to the discovery of foam cells in nine patients. Two had hereditary nephropathy and deafness; one had hereditary nephropathy alone; two had a questionable family history of renal disease; three gave no family history of renal disease; and one was thought to be an example of arabinosis. A review of the records of 105 consecutive autopsy cases of pyelonephritis uncovered six patients with renal foam cells. Only one of these had a family history of renal disease. Among this group were patients with xanthogranulomatous pyelonephritis, the de Toni-Fanconi syndrome with cystinosis, and Wegener's granulomatosis with renal abscesses.

Although renal foam cells thus are not limited to cases of hereditary nephropathy, their presence should lead to a vigorous search for a family history of renal disease.

The basic pathological picture in hereditary nephropathy with deafness is probably quite similar to that of chronic glomerulonephritis, but pyelonephritis may frequently be superimposed.

At present there is no explanation for the pathogenesis of hereditary nephropathy or renal foam cell formation.

Acknowledgment: We would like to thank the many physicians in North Carolina who forwarded information concerning family members, and especially Dr. Richard Kelly of Greensboro, North Carolina, who referred the patient to Duke Hospital with a preliminary family history. Dr. George R. Lacy, Jr., Pathologist, Memorial Mission Hospital, Asheville, North Carolina, kindly allowed us to review the renal sections originally described by Chappell and Kelsey [*19*].

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Familial Growth Retardation, Renal Aminoaciduria and Cor Pulmonale*

I. Description of a New Syndrome, with Case Reports

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THIS report presents a syndrome characterized by growth retardation, poor muscular development, scanty adipose tissue, recurrent pulmonary infection, atelectasis and right ventricular hypertrophy in three of six children of asymptomatic non-consanguineous parents. The only child to survive the first decade, who presented with small stature and muscular wasting, was found to have aminoaciduria without hyperaminoacidemia, elevated plasma unesterified fatty acid concentrations and a low basal respiratory quotient.

The excessive excretion of amino acids, while occurring in diverse conditions, is of special interest in inherited syndromes because it can provide a clue to reconstruction of the metabolic derangement and a tool for genetic investigation among asymptomatic relatives.

CASE REPORTS

CASE I. The second-born of six children, was the product of a full term uneventful pregnancy and weighed 7 pounds at birth. His rate of growth, initially normal, slowed, and at one year of age his weight was only 14 pounds despite a seemingly normal food intake. Motor development was slow; he sat alone at ten months and walked alone at two years. He was never able to sit up without first rolling to one side and assisting himself with his arms, or to climb stairs without the aid of his arms. He had a peculiar waddling gait, similar to his affected siblings. Between the ages of three (Fig. 1A) and six (Fig. 1B) his appearance became asthenic, in contrast to his unafflicted brother (Fig. 1A) who remained well. Figure 1B shows his spindly extremities at age six, compared to a normal sister, age three, when their heights were approximately equal. At age four, the patient had pneumonia and thereafter had frequent, slowly resolving infections of the respiratory tract. At age eight, he was found dead in bed, having been ambulatory with a "cold" for the preceding two weeks. Weight at the time of death was only 28 pounds.

Autopsy at the Newark State School Laboratory (50-A-2) revealed "a poorly nourished child, the musculature poorly developed, the legs appearing almost as skin and bone . . . subcutaneous fat is practically absent . . . " The left lung (Fig. 1C) weighed 95 gm., 1.5 S.D. below the mean, for this age [*7*]. Its lower lobe was bluish red, firm, and well marked off from the adjacent lighter pulmonary tissue which projected well above the firm and depressed atelectatic lobe. (Fig. 1C.) The right lung weighed 150 gm., and appeared normal. No pulmonary thrombi were present. The heart weighed 155 gm., 3 S.D. above the mean for this age, and showed marked right ventricular hypertrophy grossly and microscopically, thickening of the walls of several coronary arteries, a closed foramen ovale, and no valvular or septal defects. There was 600 ml. of clear yellow fluid in the peritoneal cavity. The liver weighed 625 gm., the spleen weighed 50 gm.; both organs showed moderate congestion grossly and microscopically. The kidneys, with a total weight of 147 gm., were normal grossly and microscopically.

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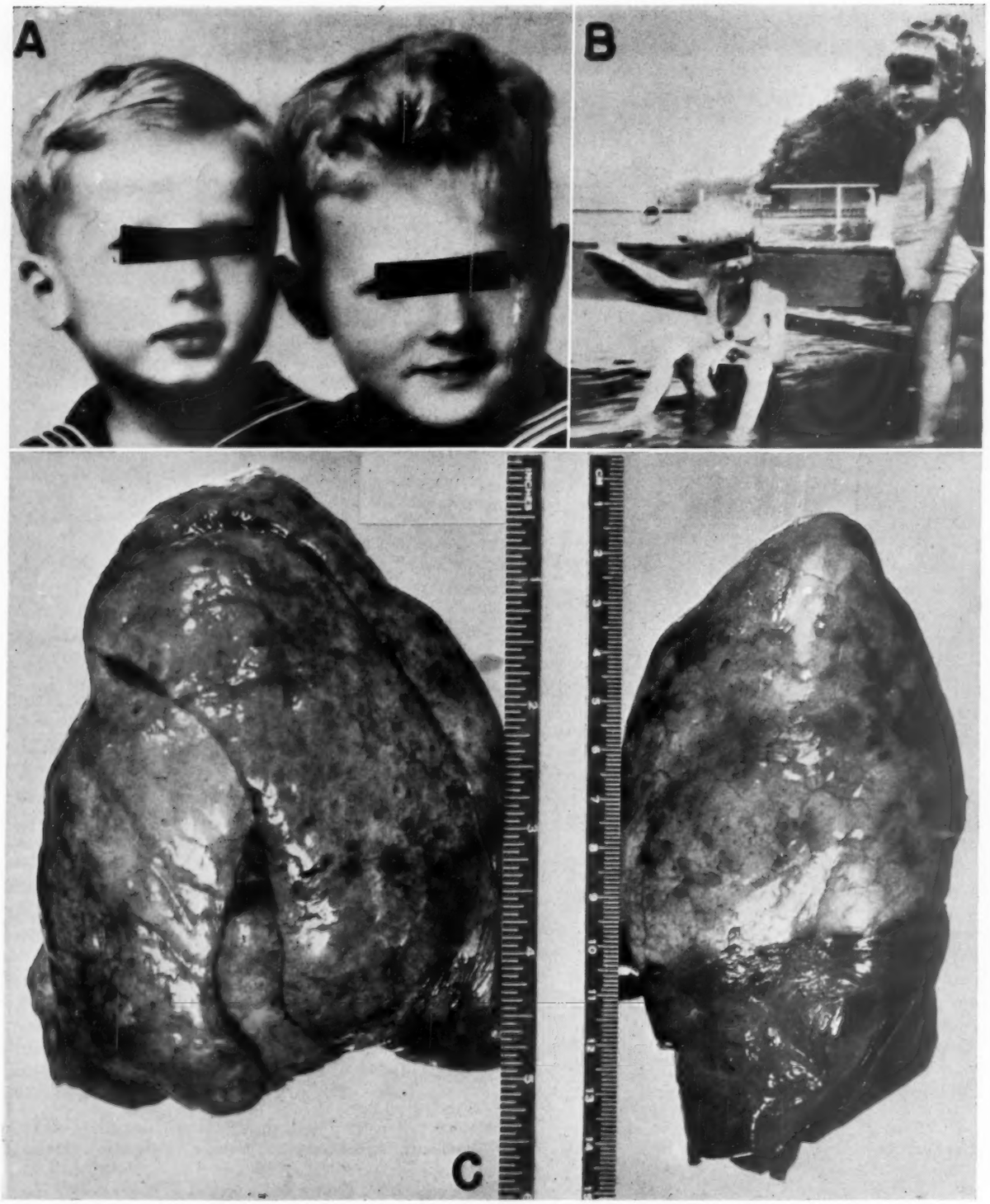


FIG. 1. Case 1. A, left, patient at age three; right, a normal sibling at age five. B, left, patient at age six; right, a normal sibling at age three. Between ages three and six patient's appearance has become markedly asthenic. C, at autopsy, left lung (shown at right) displays basilar atelectasis. Right lung is normal.

Unfortunately, no sections of lung or skeletal muscle were made. Death was ascribed to "congestive heart failure . . . due to congenital atelectasis of the left lung." Anatomic diagnoses were cor pulmonale, right ventricular hypertrophy, left lower lobar atelectasis and ascites.

CASE II. The fourth-born child, weighed 8½ pounds at birth following an uneventful pregnancy. Her weight was 28 pounds at the end of the first year, 33 pounds at the end of the second year, and 36 pounds by the seventh year, despite a food intake comparable to her normal siblings. Although the patient sat alone at six months and walked alone at fourteen months, she had difficulty sitting up and had an abnormal gait similar to her afflicted brother. She also pulled herself up stairs with her arms. By age three, she had become more slender. Her mental development was normal and she was never seriously ill, but significant thoracic scoliosis developed and she had a depressed left anterior chest. At age seven, weighing only 36 pounds, she was discovered dead at home without known prior symptoms.

Autopsy at Rochester General Hospital (472/54) disclosed "an apparently normally developed, but extremely thin and pale girl . . . with very scant subcutaneous fat." The neck veins were dilated. The sternum was depressed. The heart weighed 120 gm., 2 S.D. above the mean for this age [*7*]. The chambers of the right heart were dilated and the ventricular wall thickened to 6 mm. The left ventricular wall was 10 mm. in thickness. Microscopically, the myocardium showed foci of interstitial fibrosis and numerous Anitschkow myocytes. There was an 8 by 4 mm. atheromatous plaque present on the under aspect of the aortic leaflet of the mitral valve. The root of the aorta showed minimal streaking with longitudinal yellow atheromatous streaks. The coronary arteries were clear and the remaining valves were normal. The left lung weighed 90 gm., 1.3 S.D. below the mean for this age, and the right lung 120 gm. Purplish, rubbery areas of atelectasis involved the posterior and inferior portions of both lungs. The bronchi to the lower lobe of the right lung were moderately dilated. The trachea and the larynx showed mucosal injection and their cavities were completely filled with tenacious mucopurulent material. Microscopically, the lungs showed areas of bronchopneumonia, emphysema and atelectasis. Many of the bronchi were dilated and had thickened membranes and polypoid nodules of granulation tissue projecting into their lumens. The pulmonary vessels appeared normal. The spleen weighed 60 gm.; the liver weighed 680 gm.; these organs and the adrenals showed vascular congestion but were otherwise grossly and microscopically normal. The kidneys, with a total weight of 160 gm., were also congested, and microscopic study showed cloudy swelling. The brain appeared normal grossly and showed only meningeal congestion microscopically. Anatomic diagnoses were acute laryngotracheobronchitis, bronchopneumonia and bronchiectasis of the lower lobe of the right lung, and right ventricular hypertrophy and dilatation.

CASE III. The fifth-born child, was the product of a normal pregnancy and delivery, and weighed 9 pounds at birth. His early development was normal; he sat alone at seven months, stood alone at eleven months, walked and spoke a few words at fourteen months. However, he could rise from a supine to a sitting position only by using his arms or turning on his side. The patient weighed 23 pounds at one year and 26 pounds at eighteen months. At age twenty-two months he appeared well nourished (Fig. 2A), but his weight and height increased slowly thereafter, and he became asthenic. Since age five he had had increasingly frequent infections of the respiratory tract. Because of poor muscular development, a deltoid biopsy was performed at the Strong Memorial Hospital, Rochester, New York, at age seven and a vastus lateralis biopsy specimen was obtained on his first admission to the Clinical Center of the National Institutes of Health at age nine (see Fig. 2B for body appearance at that time); both showed only normal muscle. He was admitted for the second time to the Clinical Center four months later because of fever and a productive cough of two weeks' duration. At that time he was slightly dyspneic at rest and had difficulty coughing up his thick sputum. He had absent breath sounds and dullness over the lower field of the left lung posteriorly, and a pneumonic infiltrate was evident in the lower lobe of the left lung on roentgenograms. The temperature was 38°C. rectally. The peripheral white blood cell count was 34,500 per cu. mm. with 78 per cent neutrophils. Serum carbon dioxide content was 44 mM per L. Sputum culture failed to yield pathogenic bacteria or fungi. He was treated with tetracycline and steam inhalations, with satisfactory recovery. The full-scale Wechsler-Bellevue intelligence quotient was 107 on this admission. Four months later a short trial of parenterally administered testosterone (10 mg. twice daily) was initiated at the Johns Hopkins Hospital, without notable effect on height or weight and with equivocal improvement in muscle strength.

At age ten, he was admitted to the Clinical Center for the third time because of fever and cough of two days' duration and drowsiness for one day preceding admission. On admission, the patient was ambulatory and not in acute distress but apprehensive. The most striking feature of the patient's appearance was his small stature and asthenic habitus. (Fig. 2C.) The rectal temperature was 38.2°C., pulse was 140 per minute and regular, respirations were 44 per minute and slightly labored at rest, and blood pressure in the supine position was 90/70 mm. Hg. The height was 127 cm., weight 18 kg., both of which are below the third percentile for his age. There was a right dorsal

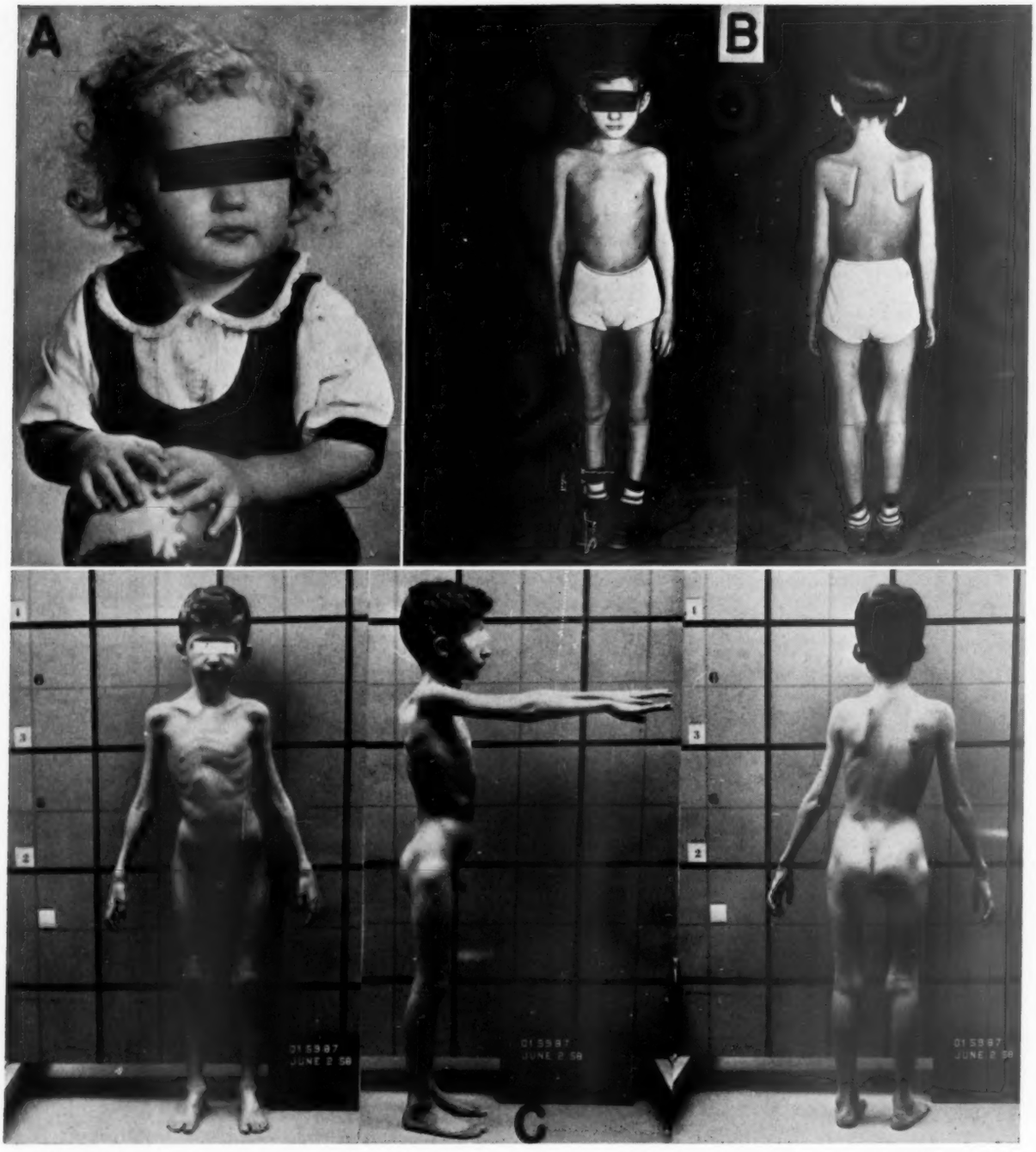


FIG. 2. Case III. A, at twenty-two months, patient appears to be in good health. B, at nine years, patient is markedly asthenic. Note winging of scapulas. C, at ten years, muscular development is still deficient, especially about the chest, and right dorsal scoliosis is increased.

scoliosis of approximately 25 degrees, without kyphosis. Muscular development was poor and subcutaneous fat deposits virtually absent, especially about the thorax and neck. There was almost no visible excursion of the chest cage on respiration. The pectoralis muscles assisted in respiration, the intercostal muscles being scarcely detectable. There was a moderate amount of fine hair over the trunk, but pubic and axillary hair was absent. The skin was dry, inelastic and sallow. Scars of previous biopsies were well healed. There was no clubbing of the digits. His voice was nasal. Cough was weak and productive of only small amounts of clear mucoid material. Breath sounds were absent and the percussion note dull over

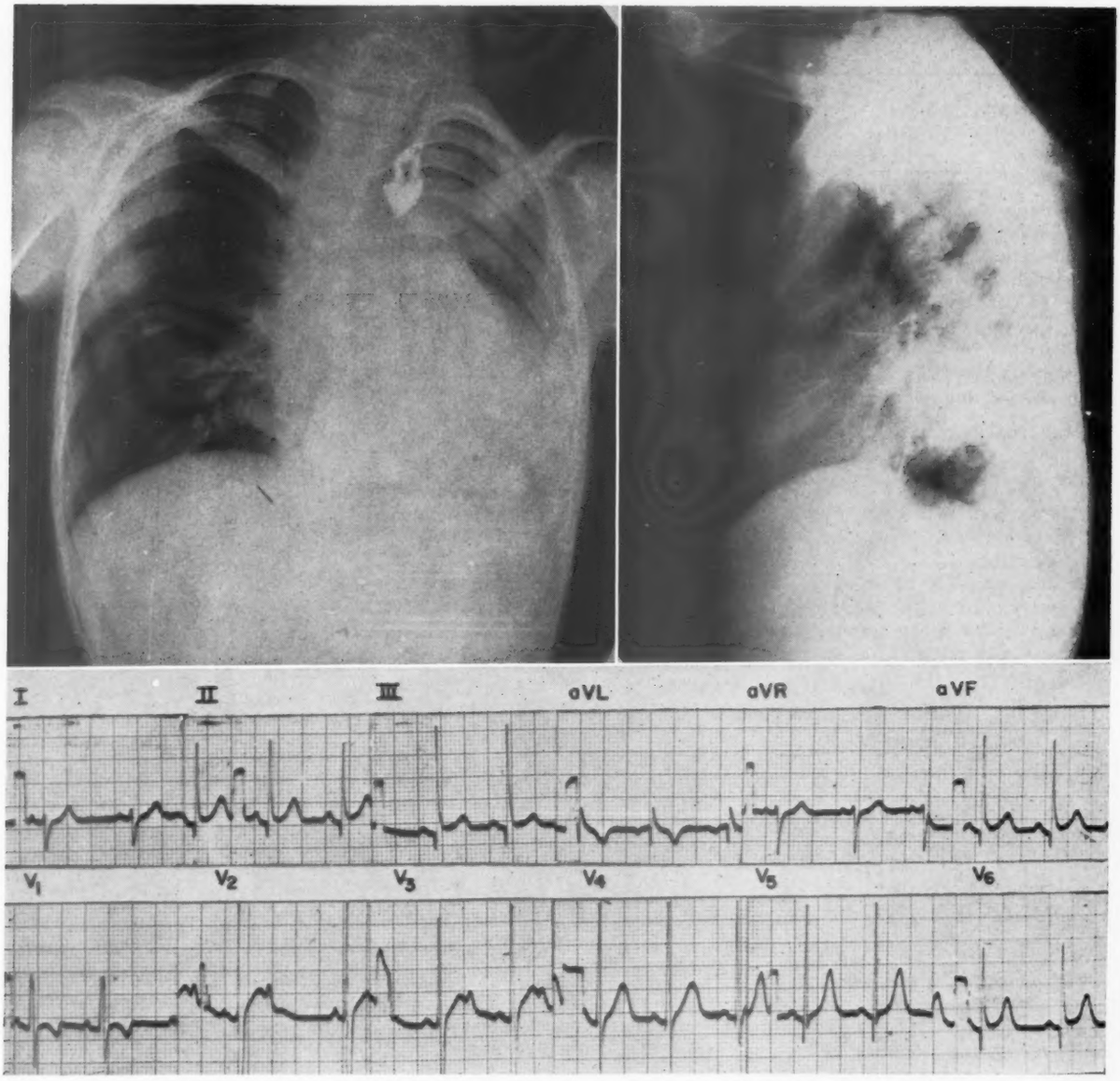


FIG. 3. Case III. Patient at age ten on third admission to the National Institutes of Health. *Top*, posteroanterior and left lateral roentgenograms of the chest showing atelectasis of lower lobe of left lung. Opacity above left clavicle is barium in the esophagus. *Bottom*, electrocardiogram showing right ventricular hypertrophy.

the lower half of the left side of the chest posteriorly, and a few scattered rhonchi were heard over the remainder of the chest. The cardiac impulse was visible as well as palpable and maximal in the left mid-clavicular line in the fourth interspace. A soft, apical, early systolic murmur was heard at times. The pulmonic second sound was loud, palpable and narrowly split; the splitting narrowed with inspiration. No thrills or diastolic murmurs were noted. The abdomen was slightly protuberant, but no liver, spleen, abnormal masses or fluid was detected. The testes were descended bilaterally and normal in size. When supine the patient was unable to lift his head from the bed or rise to a sitting position without turning to the side and using his arms. Achilles tendon reflexes were obtained on occasion, but other deep tendon reflexes were not elicited. His gait suggested a person straddling a knee-high rail.

On admission the white blood cell count was 8,900 per cu. mm. with 68 per cent neutrophils, 21 per cent lymphocytes and 11 per cent monocytes. Hemoglobin was 14.2 gm. per 100 ml.; red blood cell count 5,200,000 per cu. mm. and hematocrit 46 per cent. Erythrocyte sedimentation rate was 43 mm. in one hour (Westergren method). Urinalysis revealed no protein, sugar, acetone, cells or casts. Blood urea nitrogen was 6 mg. per 100 ml., serum sodium 143 mEq. per L., serum potassium 5.1 mEq. per L., serum

TABLE I
CARDIOPULMONARY FUNCTION (CASE III)

	Patient's Value	Normal Value
Oxygen consumption (L./min./sq. M.)		
At rest	182	160–180 [*48*]*
On exertion	305	...
Basal respiratory quotient	0.61 to 0.69	0.85 [*101*]
Ventilatory determinations		
Basal respiratory rate	26	18–22
Tidal volume (ml.)	176	328 (for height)
Minute volume (ml./min./sq. M.)	4400	...
Alveolar ventilation (ml./min.)	1900	...
Vital capacity (ml.)	630	1500 (for area) [*45*] 1800 (for height) [*45*]
Maximum breathing capacity (L./min.)	22.5	46 (for area) [*45*] 66 (for height) [*45*]
Maximum static alveolar pressure at functional residual capacity (cm. H_2O)		
Inspiratory	−95	−100 [*48*]
Expiratory	75	+125 [*48*]
Dead space (ml.)	96	⅓ tidal volume [*48*]
Effective pulmonary ventilation (ml.)	80	⅔ tidal volume [*48*]
Systemic arterial blood determinations		
Oxygen saturation (%)		
At rest	86.0	≥95
On exertion	83.5	≥95
pCO_2 (mm. Hg)	67	35–48
CO_2 content (mM/L.)	31.0	21.9
Systemic arterial pressure (mm. Hg)	90/55 (mean 75)	90–130/60–90 (mean 70–95) [*47*]
Right heart catheterization pressures (mm. Hg)		
Pulmonary wedge pressure	6/4 (mean 5)	12/3 (mean 5–12) [*46,47*]
Pulmonary artery pressure		
At rest	32/18 (mean 24)	15–30/5–10 (mean 10–20) [*47*]
On exertion	46/30	...
Right ventricular pressure	26/0	15–30/2–5 [*47*]
Right atrial pressure	3/−2 (mean 2)	6/0 (mean 1–5) [*46,47*]
Pulmonary vascular resistance (dynes-sec./cm.^{5})		
At rest	460	250 [*46*]
On exertion	552	...
Cardiac output (L./min.) at rest	2.8	3–5 [*47*]

* Numbers in brackets refer to bibliography.

chloride 93 mEq. per L., serum CO_2 content 41 mEq. per L. A chest roentgenogram (Fig. 3) showed consolidation and atelectasis of the lower lobe of the left lung with elevation of the left hemidiaphragm. There was scoliosis of the dorsal spine, resulting in a smaller hemithorax on the left than on the right. The pulmonary artery segment was somewhat prominent. Electrocardiograms (Fig. 3) showed right ventricular hypertrophy. Sputum culture revealed Neisseria catarrhalis, Streptococcus viridans and Hemophilus hemolyticus. The patient was treated with penicillin, streptomycin, potassium iodide, steam inhalations, postural drainage and mechanical exsufflation. The symptoms and fever disappeared in one week. Within two weeks the infiltrate in the lower lobe of the left lung had cleared but the atelectasis persisted. Bronchoscopy was performed and revealed only slight reddening of the mucosa of the bronchus of the lower lobe of the left lung without an intrinsic lesion or constriction. Bronchial washings contained neither acid-fast bacilli on culture nor malignant cells. Two months after the onset of symptoms the lobe was found to have spontaneously re-expanded.

After re-expansion of the atelectatic lower lobe of

TABLE II
AMINO ACIDS (CASE III)*

Amino Acid	Urine (June 3–4, 1958)				Plasma (June 18, 1958)	
	Free (mg./24 hr.)		Total (after hydrolysis) (mg./24 hr.)		(mg./100 ml.)	
	Patient	Normal†	Patient	Normal†	Patient	Normal‡
Threonine	450	28	406	74	1.22	1.39
Serine	532	43	454	113	1.09	1.12
Lysine	159	19	182	61	2.23	2.72
Arginine	66§	<10	46	<20	0.99	1.51
Tyrosine	136	35	150	75	0.92	1.03
Histidine	744	216	704	360	0.91	1.15
Alanine	90	46	96	82	1.30	3.41
Glycine (+ citrulline)	200	132	387	937	1.52	2.04
Phenylalanine	25	18	24	45	0.74	0.84
1-Methylhistidine	131	180	130	98	0	0.11
Taurine	75	156	62	210	1.37	0.55
3-Methylhistidine	25	50‖	19	...	0	0.08
Isoleucine	¶	18	¶	24	0.59	0.89
Leucine	¶	14	¶	27	1.19	1.69
Cystine	¶	<10	¶	52	0.77	1.18
Methionine	¶	<10	¶	...	0.21	0.38
Ornithine	¶	<10	¶	...	0.39	0.72
Proline	¶	<10	51	83	0.95	2.36
Valine	¶	<10	¶	30	2.18	2.88
Aspartic acid	0	<10	305	212	0.02	0.03
Glutamic acid	0	<10	1,052	531	0.36	0.70
Aminobutyric acid	?	<10‖	?	?	0.18	0.30
Total	2,633	<985	4,068	<3034	19.13	27.04

* Measured by ion-exchange chromatography, method of Moore and Stein [7].
† Average of ten normal adult males [8]. Fowler [2] found ten year old boys virtually identical with adult males.
‡ Average of five normal adult males [49]. Normal values for children approximate those for adults, according to Dustin [32].
§ Urinary arginine was normal on nine other determinations.
‖ Harris [50].
¶ Present in amounts too small to measure.

the left lung, cardiopulmonary function was studied, with results shown in Table I. His peripheral arterial oxygen saturation while breathing room air was only 86 per cent at rest and 83.5 per cent with exertion. Vital capacity (630 cc.) and maximum breathing capacity (22.5 L. per minute) were lower than the subnormal values obtained nine months previously (806 cc. and 31.0 L. per minute, respectively). A normal timed vital capacity and spirogram gave no evidence of emphysema. Because of the accentuated pulmonic second sound, the prominence of the pulmonary artery segment visible on the roentgenogram and the electrocardiographic evidence of right ventricular hypertrophy, right heart catheterization was performed. Pulmonary artery pressure was mildly elevated at rest (32/18, mean 24 mm. Hg) and increased with excitement or exercise (46/30 mm. Hg). Pulmonary vascular resistance was elevated at rest (460 dynes second per $cm.^5$) and to a lesser degree on exercise (552 dynes second per $cm.^5$); and pulmonary capillary (wedge) pressure was normal (6/4 mm. Hg). There was no evidence of a left-to-right shunt or valvular lesion using the nitrous oxide technic. Arm-to-tongue circulation time using Decholin® was normal.

A marked aminoaciduria was revealed by measuring urinary alpha-amino nitrogen excretion. In twenty-four hours the patient excreted 430 mg. of alpha-amino nitrogen (24 mg. per kg. body weight).

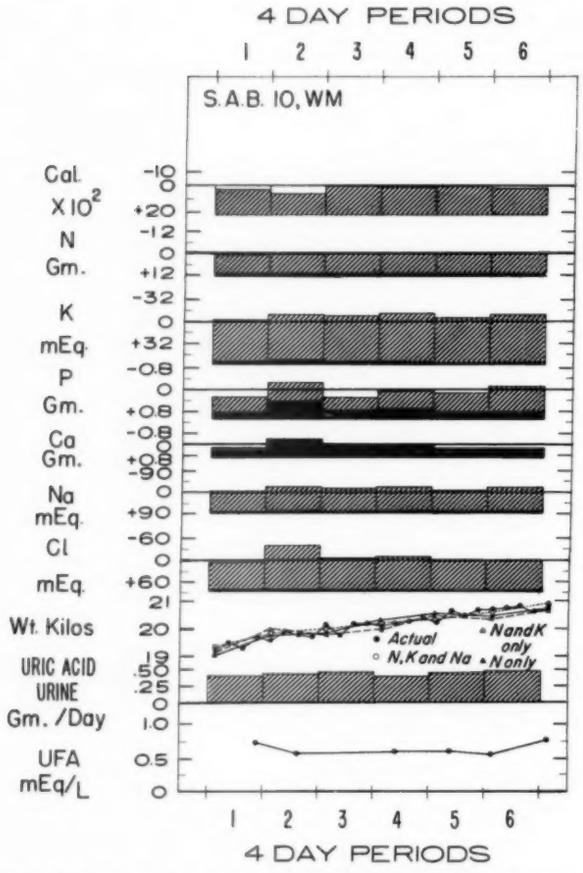


FIG. 4. Case III. On a constant diet of 2,100 calories consisting of 12 gm. nitrogen, 1,100 mg. calcium, 1,100 mg. phosphorus, 60 mEq. potassium, and 90 mEq. sodium and chloride, the patient was in positive calcium and phosphorus balance, negative sodium, potassium and chloride balance, and in positive nitrogen balance. He gained 1.5 kg. over the twenty-four-day period. Fecal losses are in black; urinary losses are cross-hatched.

Normal ten year old boys excrete a maximum of 2.5 mg. alpha-amino nitrogen per twenty-four hours [*2*].

The free amino acids excreted in greatest excess were serine, threonine, histidine, lysine and tyrosine. Fasting plasma concentration of alpha-amino nitrogen was normal. Fasting plasma concentrations of the individual free amino acids were low or normal. Urinary and plasma values on an unrestricted diet are given in Table II. Paper chromatography of the urine provided no additional information; no tryptophane or tryptophane metabolites were discovered.

The fasting plasma unesterified fatty acid concentration was markedly elevated on each of nine determinations, with a mean of 0.75 mEq. per L. (normal value 0.35 mEq. per L., S.D. 0.12). In addition, the basal respiratory quotient was low, 0.61 to 0.69.

Spontaneous twenty-four-hour creatinine excretion was 217 mg. total or 11.4 mg. per kg. of body weight, compared to 16 to 18 mg. per kg. for normal ten year old boys.

Roentgenograms showed minimal osteoporosis, a bone age at the lower limits of normal and a normal sella turcica.

The remainder of the laboratory investigation was within normal limits. The serum calcium was 10.7 mg. per 100 ml., serum phosphorus 4.5 mg. per 100 ml. Serum alkaline phosphatase was 4.2 Bodansky units. A reaction to the Sulkowitch test for calcium in the urine was 3 plus. Serum protein-bound iodine was 5.1 μg. per 100 ml. (normal, 4 to 8 μg. per 100 ml.). Serum albumin was 4.1 gm. per 100 ml., serum globulin 3.7 gm. per 100 ml. Serum gamma globulin (by precipitation) was 1.3 gm. per 100 ml. (normal, 0.6 to 1.4 gm. per 100 ml.). Serum mucopolysaccharide and seromucoid concentrations were reduced. Serum protein electrophoresis showed a normal pattern. The reaction to the cephalin flocculation test was 1 plus, thymol turbidity 2 plus. Blood ammonia concentrations varied from 30 to 196 μg. per 100 ml. (normal, less than 100 μg. per 100 ml.). The serum total bilirubin was 0.1 mg. per 100 ml. An oral glucose tolerance test (0.75 gm. per kg. body weight) was normal: fasting, 80 mg. per cent; one-half hour after the administration of glucose, 187 mg. per cent; at one hour, 191 mg. per cent; at one and a half hour, 179 mg. per cent; at two hours, 121 mg. per cent; at three hours, 73 mg. per cent and at four hours, 81 mg. per cent. Each of the corresponding urine samples following the administration of glucose showed a trace of reducing substance. Chromatography of the urine showed no galactose.

The serum total cholesterol was 158 mg. per 100 ml., free cholesterol 38 mg. per 100 ml. The serum phospholipid concentration was 195 mg. per 100 ml., serum triglycerides 49 mg. per 100 ml. Fecal excretion of orally administered I^{131}-labeled triolein was 0.8 per cent (normal, 0 to 5 per cent). Fecal fat was not increased (Sudan stain). The plasma 17-hydroxycorticoid concentration was 11 μg. per 100 ml. (normal, 4 to 10 μg. per 100 ml.). Urinary 17-hydroxycorticoid excretion per twenty-four hours measured 3.3 mg. (normal, 4 to 10 mg.).

A "sweat test" revealed normal concentrations of sodium, potassium and chloride. Trypsin was present in the stool.

During this admission the patient was placed on a constant diet of 2,100 calories consisting of 12 gm. nitrogen, 1,100 mg. calcium, 1,100 mg. phosphorus, 60 mEq. potassium and 90 mEq. sodium and chloride for twenty-four days. Urinary and fecal losses were measured during each of the six four-day periods, as shown in Figure 4. During this period the patient gained 1.5 kg. He was in positive calcium and phosphorus balance, in negative sodium, potassium (8 mEq. per day) and chloride balance, and in positive nitrogen balance (plus 0.75 gm. per day). The urinary uric acid excretion was 450 to 500 mg. per day.

Examination exactly one year later, at age eleven,

revealed a loss of 1.3 kg. body weight, yet a 2 cm. gain in height and a fully normal bone age. The patient had no serious infections of the respiratory tract during this period.

SUMMARY OF CASES

In three of six children of asymptomatic, unrelated parents growth retardation was manifested and an asthenic habitus developed with poor muscle development and scanty adipose tissue beginning in the first or second year of life. Two died suddenly at ages eight and seven years, respectively, and were found at autopsy to have basilar atelectasis and right ventricular hypertrophy. One, living at age eleven, presents a history of recurrent pneumonia with atelectasis, clinical evidence for right ventricular hypertrophy, elevated pulmonary artery pressure on exertion, renal aminoaciduria, increased plasma unesterified fatty acid concentration and a low basal respiratory quotient. (Table III.)

TABLE III
SUMMARY OF CASES

	Case No.		
	I	II	III
Clinical features			
Growth retardation; reduced muscle and adipose tissue	+	+	+
Pulmonary infection and atelectasis	+	+	+
Right ventricular hypertrophy	+	+	+
Chemical features			
Aminoaciduria	?	?	+
Increased serum unesterified fatty acids and decreased respiratory quotient	?	?	+
Course	Died, 8 yr.	Died, 7 yr.	Living, 11 yr.

COMMENTS

Aminoaciduria. The urinary alpha-amino nitrogen excretion in Case III (24 mg. per kg. body weight per twenty-four hours) is nearly ten times the normal value for ten year old boys (2.5 mg. per kg. body weight per twenty-four hours) [*2*]. Reference of urinary alpha-amino nitrogen excretion to creatinine excretion, as recommended by Fowler [*2*], is misleading in the present case because creatinine excretion was itself diminished, no doubt due to the disproportionate reduction in muscle bulk.

Table IV presents a classification of pathologic states associated with aminoaciduria together with a list of the amino acids excreted and the principal clinical features in each. It is apparent that the present syndrome closely resembles none of these. Professor C. E. Dent, who has reviewed the data in this family, has seen no similar case.

Dent [*3*] has distinguished "overflow" and "renal" types, the former due to increased plasma amino acid concentration, the latter due to a primary defect in renal tubular reabsorption. As a first approximation, an aminoaciduria may be classified as "renal" if the plasma concentrations of the amino acids excreted in excess are normal or low. Renal clearance determinations are desirable for definitive evaluation, however, because excessive excretion of those amino acids which normally have relatively high renal clearances may result from very slight elevations in plasma concentrations. Plasma levels of all measured amino acids except taurine are low or normal in Case III. Endogenous amino acid clearance studies have recently confirmed the "renal" basis for the aminoaciduria [*11*].

Inherited renal aminoacidurias (II-B, Table IV) may be subdivided into primary and secondary types [*4*]. An aminoaciduria may be termed "secondary" if it results from the abnormal accumulation in the renal tubule of "toxic substances," as in galactosemia [*5*] and Wilson's disease [*6*]. It should be stated, however, that this classification is theoretical at the present time because the exact nature of the toxic substance or substances is unknown. There is no evidence of galactosemia or Wilson's disease in the present case, and no abnormal metabolite has been demonstrated. We have therefore tentatively classified the present syndrome as "primary" or idiopathic.

The pattern of urinary amino acid excretion in Case III, shown in Table II, was obtained by the column chromatographic technic described by Moore and Stein [*7*]. Eleven free amino acids are regularly excreted in excess. Dividing the amount of each excreted per kilogram of body weight by the value for a normal male [*8*] yields the following ratios: threonine 61, serine 47, lysine 23, arginine 25, tyrosine 15, histidine 13, alanine 7.4, glycine 5.7, phenylalanine 5.2, 1-methylhistidine 2.7, and taurine 1.8. Of the

TABLE IV

PATHOLOGIC STATES WITH AMINOACIDURIA*

Name and Provisional Classification	Reference	Excreted in Excess†	Principal Clinical Features‡
I. Overflow type			
(A) Acquired			
(1) Liver damage	Walshe [53]	General	...
(2) Brief starvation	Sandler, Pare [84]	β-AB	...
(B) Inherited			
(1) Phenylketonuria	Knox, Hsia [56]; Evered [9]	Phenylalanine (C), phenylpyruvate, phenyllactate, phenylacetate, phenylacetylglutamine, o-hydroxyphenylacetate, indolylacetate, indolyllactate	Mental deficiency, fair hair and skin, blue eyes, involuntary movements, dermatitis, autosomal recessive inheritance
(2) Maple syrup disease	Westall et al. [58]; Menkes [59]	Val, leu, ileu, (α-ketoisocaproic acid, α-ketoisovaleric acid, α-keto-β-methyl-n-valeric acid)	Progressive spasticity, myoclonic seizures, occurrence in siblings
(3) Cystathioninuria	Harris [60]	Cystathionine	Mental deficiency, cystathionine deposits in liver and kidney
(4) Argininosuccinic aciduria	Allan et al. [57]; Cusworth, Dent [17]	Argininosuccinic acid (C)§	Seizures, mental retardation, ataxia, friable hair, occurrence in siblings
(5) Hypophosphatasia	Cusworth, Dent [17,61]	Phosphoethanolamine (C)§	Retarded bone growth, nephrocalcinosis, decreased tissue and serum alkaline phosphatase, autosomal recessive inheritance
(6) β-amino*iso*butyric aciduria	Crumpler et al. [13]; Evered [9]	β-AB (C)§	Asymptomatic
II. Renal type			
(A) Acquired			
(1) Vitamin deficiencies			
(a) Scurvy	Jonxis, Wadman [14]; Huisman, [15]	Ser, thr, gly, ala, tau, tyr, his, lys, β-AB, bound glu	...
(b) Rickets	Huisman [15]; Jonxis et al. [16]; Cusworth, Dent [17]	Ser, thr, gly, ala, his, lys, bound gly (C)	...
(c) Vitamin E deficiency (in rabbits)	Dinning [68]	General	...
(2) Potassium deficiency	Denton et al. [69]; Davidson et al. [70]	General	...
(3) Kwashiorkor	Schendel et al. [51]; Dubois et al. [52]	General, especially β-AB, tau, his	...
(4) Poisons			
(a) Cadmium	Clarkson, Kench [18]	Thr, ser, (gly, ala, glutamine, tyr, lys, his, methyl his, cys, val, try)	...
(b) Uranium	Clarkson, Kench [18]; Voegtlin, Hodge [19]	Thr, ser, glutamine, (ala, val, asparagine, tyr, lys, his, methyl his)	...
(c) Lead	Clarkson, Kench [18]; Marsden, Wilson [20]; Chisholm et al. [21]	Ala, β-AB, (thr, methyl his, tyr, ser, tau, glutamine, lys, leu, glu, asp, gly)	...
(d) Mercury	Clarkson, Kench [18]	Gly, (glu)	...
(e) Nitrobenzene	Parker, Neill [65]	General, especially ala, glutamine, ser, gly, tau, tyr, glu, β-AB	...
(f) Lysol	Spencer, Franglen [66]	General	...
(g) Maleic acid (in rats)	Harrison, Harrison [67]	Leu, ileu, val, met, his, ala, glu. Also phosphate, glucose	...

*See footnotes on page 198.

TABLE IV (*Continued*)
PATHOLOGIC STATES WITH AMINOACIDURIA*

Name and Provisional Classification	Reference	Excreted in Excess†	Principal Clinical Features‡
(5) Acute tubular necrosis	Emslie-Smith et al. [72]	General	...
(6) Nephrotic syndrome	Woolf et al. [86]; Hooft, et al. [87,88]	"R pattern": pro, leu, val, ala; "H pattern": ethanolamine, β-AB, tau, tyr, leu, val. Also protein, glucose, phosphate, potassium	...
(7) Multiple myeloma	Engle, Wallis [71]	General, especially gly, ala, glutamine, cys, lys, ser, citrulline. Also glucose, phosphate.	...
(B) Inherited			
(1) Primary or unknown			
(a) Cystinuria	Stein [73]; Robson, Rose [23]; Arrow, Westall [24]	Lys, arg, cys, orn (C)	Urolithiasis
(b) Cystinosis	Evered [9]	Gly, ser, arg, thr, ala, tyr, lys; (leu, ileu, val, met, phe, cys, pro) (C). Also glucose, phosphate, potassium	Vitamin D-resistant rickets or osteomalacia; chronic renal acidosis; hypophosphatemia; swan-neck segment of renal tubules; cystine deposits in liver, spleen, marrow, lymph nodes, kidney, subcutaneous tissue, cornea; autosomal recessive inheritance
(c) Adult Fanconi syndrome	Evered [9]; Wallis, Engel [29]; Cusworth, Dent [17]	Same as cystinosis (C)	Same as cystinosis except no tissue deposits of cystine and frequent non-familial occurrence
(d) Renal glycosuria and aminoaciduria without hypophosphatemia	Luder, Sheldon [74]	Pro, leu, val, (cys, lys, tyr, ser, thr, ala, glutamine, β-ala, α-AB, met). Also glucose, fructose, protein	Growth retardation, autosomal dominant inheritance
(e) Congenital renal tubular acidosis	Harrison [75]	Lys, ala, asparagine, thr, tyr, gly, glu, his, arg, α-aminoadipic acid, tau, val, leu, ileu, phe, β-AB, ser. Also phosphate	Renal acidosis and hypophosphatemic rickets without glycosuria
(f) Buphthalmos and organic aciduria	Lowe et al. [76]	Gly, ser, lys, ala, val, asp, glutamine, leu, his. Also organic acids, phosphate, calcium, protein	Mental and physical retardation, cataracts and glaucoma, renal tubular acidosis, osteomalacia and rickets, sex-linked inheritance
(g) Hartnup disease	Baron, et al. [77]; Jepson [78]; Evered [9]	Ala, ser, asparagine, glutamine, val, leu, ileu, phe, tyr, try, his, (cys, lys, gly) (C). Also indoxyl sulphate, 3-indolylacetic acid, N-(3-indolylacetyl)glutamine	Pellagra-like skin rash on exposure to sunlight, intermittent cerebellar ataxia, mental deterioration, increased fecal protoporphyrin, autosomal recessive inheritance
(h) Sex-linked microcephaly and spastic diplegia	Paine [79]	Generalized	Microcephaly, mental retardation, spastic diplegia, cerebellar hypoplasia, sex-linked recessive inheritance

*See footnotes on page 198.

TABLE IV (*Continued*)
PATHOLOGIC STATES WITH AMINOACIDURIA*

Name and Provisional Classification	Reference	Excreted in Excess†	Principal Clinical Features‡
(i) Familial convulsive disorder	Joseph et al. [80]	Especially proline	Progressive convulsive disorder of infancy with increased spinal fluid protein, occurrence in siblings
(j) Baber's congenital cirrhosis	Baber [81]	General, especially tyr, ser, thr, his, try, met, lys. Also glucose, phosphate, potassium, urobilinogen	Growth retardation, portal cirrhosis, vitamin D-resistant rickets, steatorrhea
(2) Secondary			
(a) Hepatolenticular degeneration	Stein et al. [6]	Thr, cys, ser, gly, asparagine, glutamine, val, tyr, lys, (his, orn, phe, pro, citrulline)	Tremor, dementia, Kayser-Fleischer ring, hepatic cirrhosis, decreased serum ceruloplasmin, autosomal recessive inheritance
(b) Galactosemia	Holzel et al. [22]	Ser, gly, ala, thr, val, (lys, cys, tyr, glu, phe) (C)	Physical and mental retardation, vomiting, diarrhea, cataracts, jaundice, improvement on galactose-free diet, autosomal recessive inheritance
(C) Heritability unknown			
(1) Idiopathic osteomalacia with glycinuria	Evered [9]; Dent, Harris [96]; Cusworth, Kench [17]	Gly (C) (pro, 1-methyl his); also phosphate	Severe osteomalacia moderately resistant to vitamin D
III. Combined type			
(1) Pregnancy	Wallraff et al. [82]; Page et al. [83]	His (C), bound try, thr, try, phe, bound glu, arg, ser, tyr	...
IV. Unclassified			
(1) Oasthouse disease	Smith, Strang [93]	Phe, met, tyr, α-hydroxybutyric acid, phenylpyruvic acid, phenylacetic acid	Mental deficiency, muscular flaccidity, recurrent pyrexia with generalized edema, pungent urine odor

* Instances of aminoaciduria have been reported in the following conditions: acute intermittent porphyria [89], congenital hemolytic anemia [90], Fanconi's anemia [64,91], vitamin B_{12} deficiency [97], rickets with vitamin D_2 hypersensitivity [98], osteopetrosis [63], gargoylism [63,92], progressive muscular dystrophy [94], march hemoglobinuria [95], progeria [99], tryosinosis [100], familial and sporadic pancreatitis [54], idiopathic hypoproteinemia [62–64], dehydration in infants [55], hyperadrenocorticism [25–28], surgery [26], and burns [26,85].

† Symbols: α-AB = α-amino-n-butyric acid; β-AB = β-amino*iso*butyric acid; ala = alanine; arg = arginine; asp = aspartic acid; cys = cystine; glu = glutamic acid; gly = glycine; his = histidine; ileu = isoleucine; leu = leucine; lys = lysine; met = methionine; orn = ornithine; phe = phenylalanine; pro = proline; ser = serine; tau = taurine; thr = threonine; try = tryptophane; tyr = tyrosine; val = valine. Amino acids excreted excessively but to a lesser degree are enclosed in parentheses. *Bound* refers to increment after hydrolysis. (C) indicates that data on renal clearance is available.

‡ Clinical features are listed for only the less common disorders.

§ There is at present no definite evidence that these amino acids are reabsorbed by the normal renal tubule [17].

amino acids excreted in bound form (calculated by subtracting the amount excreted in the free form from the total amount after hydrolysis), glutamic acid is also excreted in excessive amounts. The urinary amino acid excretion can be analyzed either by scrutinizing the amino acids excreted in excess for similarity of chemical structure or metabolic fate or by comparing the over-all pattern with that seen in other pathologic states with aminoaciduria.

The amino acids excreted in excess have no apparent structural similarity. Neither is there an obvious similarity in origin or metabolic pathway. The mean of their renal clearances [*9*] is 3.08 ml. per minute, exceeding the mean for the renal clearances of the amino acids not excreted in excess which is 0.67 ml. per minute. They have been referred to as the "central cluster" because of their central location on paper chromatograms [*10*]. It is not possible to explain the aminoaciduria in this case by a defect in a single renal transport mechanism, as has been proposed for cystinuria [*12*].

The amino acid excretion pattern mentioned may be compared with those of the pathologic states listed in Table IV. It bears a similarity to those of scurvy [*14,15*], rickets [*15–17*], heavy metal poisoning [*18–21*], and galactosemia [*22*]. The present case resembles none of these conditions in respect to principal clinical, laboratory or roentgenologic features. An important difference in urinary excretion between cystinosis and the adult Fanconi syndrome, on the one hand, and the present case (Case III), on the other, is the absence of glycosuria, hyperphosphaturia and defective urinary acidification.

Since free amino acids are known to be filtered at the glomerulus, differences in renal clearances would seem to reflect differences in tubular reabsorption. Factors known to affect the tubular reabsorption of the amino acids which are excreted in excess in the present case include heredity, sex, age, diet, state of nutrition, and other substances in the glomerular filtrate which compete for reabsorption. Genetic factors affect the tubular reabsorption of glycine and taurine [*9,30*]. Males have been observed to excrete more serine and valine but less β-alanine and β-amino*iso*butyric acid than females [*31*]. Dustin [*32*] and Fowler [*2*] have noted increased excretion of nearly all the commonly found amino acids in the newborn and especially in the premature infant. A high protein diet is known to increase excretion of 1-methylhistidine [*9*]. None of these factors appears to be playing a significant role in the excretion pattern in Case III. Loeb [*33*] noted that in the underweight child, amino acid excretion may be slightly increased compared to the normal mean based on the subject's ideal weight. Although this factor could conceivably be playing a minor role in the present case, the order of magnitude of the aminoaciduria precludes this as the principal cause.

Finally, the tubular reabsorption of a given amino acid is influenced by other amino acids in the glomerular filtrate. This has been demonstrated in dogs by Pitts [*34*], Beyer [*35*] and Kamin [*36*]. Dent and Rose [*37*] have postulated a common reabsorptive mechanism for cystine, lysine, arginine and ornithine because of excessive excretion of all four by many patients with cystinuria. The diffuse character of the aminoaciduria in the present case suggests a generalized defect in tubular reabsorption of amino acids, but proof of any specific defect is lacking at present.

Elevated Plasma Unesterified Fatty Acids. In Case III the patient had consistently elevated fasting plasma unesterified fatty acid concentrations and a low basal respiratory quotient (0.61 to 0.69) despite a daily caloric intake of over 100 calories per kg., or nearly twice the normal intake for a child of his age. There was no evidence of intestinal malabsorption.

Common causes of an increased plasma unesterified fatty acid concentration are as follows: fasting, hyperthyroidism, acute psychic stress, injections of heparin, epinephrine, norepinephrine, or growth hormone, diabetes mellitus, rapid tumor growth or simple obesity [*38*]. In Case III, repeated basal metabolic rate and thyroid function studies were within normal limits. An attempt was made to minimize anxiety during venipunctures. The patient received no heparin, epinephrine or growth hormone injections. Results of glucose tolerance tests, fasting blood glucose determinations and urinalyses for reducing substances were within normal limits. Neoplastic growth and obesity are not operative in this patient. In short, the reason for this patient's increased fat mobilization remains unexplained. It might be speculated that the patient, in view of his defect in growth, secretes an excess of some growth hormone-like substance. This situation would be analogous to overproduction of other pituitary hormones in conditions of target organ failure, e.g., the

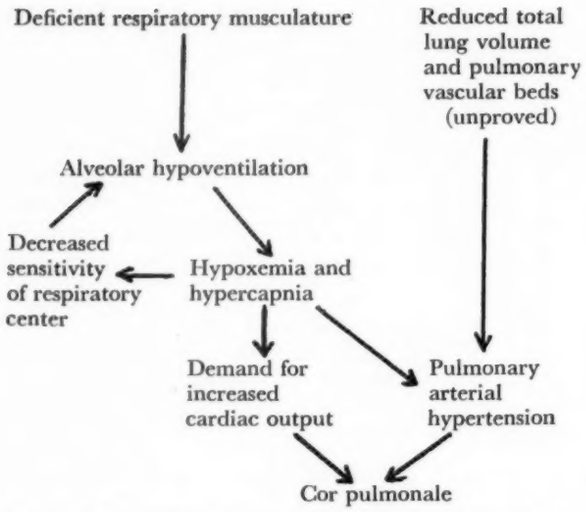


FIG. 5. Hypothetical scheme of the pathogenesis of cor pulmonale in Case III.

eunuchoid overproduction of follicle-stimulating hormone.

Cardiorespiratory Abnormalities. Comparison of the weights of individual organs in Cases I and II with the normal values for their respective ages [*1*] reveals that the left lung in each case was small, whereas weights for the right lung, liver, spleen and kidneys were near the normal values. Atelectasis and infection involved the basilar portion of the left lung in each of the three cases.

The elevated arterial pCO_2 and arterial hypoxemia seen in Case III suggest the "alveolar hypoventilation syndrome" [*39*]. The other two major causes of arterial hypoxemia are a right-to-left shunt and alveolar-capillary block. A significant right-to-left shunt is excluded by the cardiac catheterization dye studies. Uncomplicated alveolar-capillary block is also unlikely since it is normally accompanied by a normal or decreased, rather than an increased, arterial pCO_2. His poorly developed chest musculature decreases his capacity to perform ventilatory work. Muscular weakness has been documented as the cause of the alveolar hypoventilation syndrome in other diseases, e.g., in poliomyelitis [*40*], amyotrophic lateral sclerosis [*41*], and myotonic dystrophy [*42*]. The hypercapnia and hypoxemia resulting from chronic alveolar hypoventilation decrease the sensitivity of the respiratory center, and ventilation becomes even more inadequate. The pulmonary arterial hypertension in Case III is very likely due to chronic hypoxemia and permanent pulmonary parenchymal damage. If, like Cases I and II, he has small lungs, a reduced pulmonary vascular bed may also contribute. The pulmonary arterial hypertension, in conjunction with the demand for an increased cardiac output necessitated by the hypoxemia, is probably responsible for the cor pulmonale. A hypothetical scheme of the pathogenesis of the cor pulmonale is shown in Figure 5.

Deficient musculature is no doubt responsible in this case for weak cough and perhaps for frequent and slowly resolving infections of the respiratory tract with atelectasis and potential destruction of lung parenchyma.

Severe kyphoscoliosis may cause alveolar hypoventilation and cor pulmonale. However, the 25 degree right dorsal scoliosis in Case III would not be sufficient to explain the magnitude of the cardiopulmonary dysfunction noted [*43*].

Growth Retardation. Growth retardation beginning during the first years of life, with poor muscular development and scanty adipose tissue, was striking in all three subjects. The cause is entirely unknown. At the age of one year all three patients became increasingly thin and took on a marasmic appearance despite a seemingly adequate food intake. Autopsy examination in Cases I and II showed virtual absence of subcutaneous and other fat deposits.

This syndrome resembles progeria in certain respects, i.e., marked growth retardation, scant subcutaneous fat, normal intelligence, aminoaciduria and sudden death at an early age; it lacks, however, the baldness, the characteristic facies, skeletal abnormalities and atherosclerosis as the cause of death.

Although in Case III the patient excretes excessive amounts of amino acids, including three essential amino acids, *viz.*, lysine, threonine and phenylalanine, it is doubtful that specific amino acid deficiency or deficiencies would account for the observed growth retardation while the protein intake was adequate. Although the pattern of the aminoaciduria resembles those of scurvy and of rickets, bone growth roentgenologically appeared nearly normal and the usual accompanying clinical and chemical features of each of these disorders are missing. It is difficult to assess the role of chronic alveolar hypoventilation since it is not known whether it preceded the onset of growth retardation. Chronic pulmonary infection does not by itself seem an adequate explanation, since the children were entirely asymptomatic between acute

infections of the respiratory tract. Fibrocystic disease of the pancreas and agammaglobulinemia, which are causes of recurrent pulmonary infection and growth retardation, were excluded in Case III, as were other causes of dwarfism, *viz.*, chronic anemia, renal acidosis, a congenital intracardiac shunt and premature epiphyseal closure. There was no evidence for hypofunction of pituitary, thyroid or parathyroid glands.

The significance of decreased serum mucopolysaccharides and seromucoids is not known. Low levels occur in normal infants, in patients with liver disease, and in starved rats; many diseases are associated with increased levels [*44*].

Growth retardation, decreased muscle mass and frequent infections of the respiratory tract may all be due to a primary defect in protein synthesis, but no such defect has been discovered. Excessive fat utilization, as indicated by the increased plasma unesterified fatty acid concentration and low respiratory quotient, is unexplained.

Inheritance. The florid syndrome has occurred in three of six siblings. The father (age thirty-nine), the mother (age thirty-seven), two brothers (ages eighteen and four), and one sister (age thirteen) are normal in height and weight, have had recent chest roentgenograms with no abnormal findings, and are without symptoms. Except for the maternal grandmother, said to have died of a heart attack at age sixty-two, there is no family history of cardiac, pulmonary or renal disease, nor is there a family record of growth retardation. There is no known consanguinity.

SUMMARY

A syndrome, apparently previously undescribed, characterized by growth retardation, poor muscular development, scanty adipose tissue, recurrent pulmonary infection, atelectasis and right ventricular hypertrophy has been found in three of six children of asymptomatic parents. Two children died suddenly in the first decade. The survivor has, in addition, aminoaciduria without hyperaminoacidemia, increased plasma unesterified fatty acid concentration, a low basal respiratory quotient and evidence of alveolar hypoventilation with resultant cor pulmonale.

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A New Syndrome: Familial Growth Retardation, Renal Aminoaciduria and Cor Pulmonale*

II. Investigation of Renal Function, Amino Acid Metabolism and Genetic Transmission

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IN the preceding publication from this laboratory [*1*], a previously undescribed familial syndrome characterized by dwarfism, hypoplastic somatic musculature, aminoaciduria and cor pulmonale secondary to alveolar hypoventilation was described. Detailed case reports of the afflicted members of the family were presented, as were the biochemical abnormalities exhibited by the ten year old white male propositus of the study. In this report we have considered in greater detail the metabolic abnormalities present in this disorder. Investigations of the propositus, his family, and closest relatives have been undertaken in an attempt to gain further insight into the etiology, pathogenesis and familial expression of this syndrome.

The propositus was originally studied at the National Institutes of Health in 1957. His clinical course has changed very little from that described previously [*1*]. At the time of this writing he is twelve years old; his height is 135 cm. and his weight 25.3 kg. He has grown 8 cm. in height and has gained 7 kg. in weight in the three-year interval, but remains in the first to third percentile for body height and weight. The hypoplastic somatic musculature and the scoliosis previously described have changed very little. Cardiopulmonary findings have been remarkably stable and no evidence of congestive failure or secondary polycythemia have appeared despite diminished alveolar ventilation, chronic hypoxemia and persistent hypercapnia. He continues to be alert and of normal intelligence. Repeated physical examinations and laboratory studies have revealed no findings which would enable us to identify the disorder as a previously described entity.

MATERIAL AND METHODS

All data referable to renal function, amino acid metabolism and metabolic balance studies were collected while the patient was hospitalized at the Clinical Center, National Institutes of Health, between May 1959 and June 1960. When not actively studied, he was followed in the outpatient clinic, and his diet and activity were controlled as necessary.

The six year old brother of the propositus was also admitted to the Clinical Center for observation, but all other family members were studied as outpatients.

The twenty-four hour urine samples, obtained from the immediate family and relatives, were collected personally by two of us (L. E. R. and P. S. M.). The urine samples were measured, aliquots were taken and frozen within twenty-four hours after collection to prevent bacterial contamination. The frozen aliquots were then returned to the National Institutes of Health for analysis.

Plasma and urinary alpha-amino nitrogen concentrations were determined by the ninhydrin-CO_2

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TABLE I
EVALUATION OF RENAL FUNCTION

Test	Patient	Normal Values
Urine pH	4.0–6.0	4.0–7.0
Proteinuria	Negative	Negative
Glycosuria	Negative	Negative
Concentration (Fishberg)	1.027	1.022–1.030
Dilution (Fishberg)	1.005	1.002–1.006
Phenolsulfonphthalein excretion	80% in 2 hr.	55–90% in 2 hr.
Blood urea nitrogen (mg. %)	9–11	9–15
Intravenous pyelogram	Normal	...
Alpha-amino nitrogen (mg./kg./24 hr.)	13.6	2.0
Urea clearance (2 hr. collection) (cc./min./1.73 M^2.)	135	75
Creatinine clearance (2 hr. collection) (cc./min./1.73 M^2.)	165	125
Inulin clearance (cc./min./1.73 M^2.)	256	127
Total titratable acid (mEq./kg./24 hr.)	0.4	0.2–0.5
Urinary ammonia (mg./24 hr.)	Approx. 500	Approx. 400–700
Organic acid excretion (mEq./kg./24 hr.)	1.4	ca 1.0

method [2,3]. Quantitative determinations of individual free amino acids in plasma and urine were obtained by the column chromatographic technic of Moore, Spackman and Stein [4]. The following analytical methods were employed: dietary, urinary and fecal nitrogen, macrokjeldahl [5]; uric acid, enzymatic method of Praetorius [6]; creatinine, Bonsnes and Taussky modification of the Jaffé reaction [7]; total titratable acidity of urine, Folin method [8]; urinary organic acids, Van Slyke and Palmer method [9]; urinary ammonia, Malfatti formol titration [10].

INVESTIGATIONS AND RESULTS

Renal Function. Twenty-four hour urine volume ranged between 800 and 2,000 cc. depending on water intake. Urine pH was consistently between 5 and 6. Proteinuria and glycosuria were never observed. Table I summarizes the data on renal function. Concentration, dilution and phenolsulfonphthalein tests all yielded normal results. The blood urea nitrogen ranged between 9 and 11 mg. per cent. An intravenous pyelogram showed normal function bilaterally. Determination of twenty-four hour urinary total titratable acid and organic acids was within normal limits. Determination of twenty-four hour urinary ammonia was slightly elevated, probably related to the chronic respiratory acidosis. Twenty-four hour urinary excretion of alpha-amino nitrogen averaged about 340 mg. per twenty-four hours or 13.6 mg. per kg. per twenty-four hours (normal 2 mg. per kg. per twenty-four hours). Two hour endogenous creatinine clearance (165 cc. per minute per 1.73 M^2. and urea clearance (134 cc. per minute per 1.73 M^2.) were significantly greater than normal suggesting a high glomerular filtration rate (GFR), and this was corroborated by a standard inulin clearance of 250 cc. per minute per 1.73 M^2. The C urea:C inulin ratio of 0.525 was normal. The PAH clearance was not determined.

TABLE II
BREAKDOWN OF TWENTY-FOUR HOUR URINARY NITROGEN

Compound	Urinary Excretion (gm./24 hr.)	Per cent of Total Excretion
Total urine nitrogen	7.80	100.0
Urea nitrogen	5.99	76.7
Creatinine nitrogen	0.13	1.6
Creatine nitrogen	0.18	2.3
Uric acid nitrogen	0.15	1.9
Alpha-amino nitrogen	0.34	4.3
Ammonia nitrogen	0.50	6.4

Table II gives a complete breakdown of the urinary nitrogen from a single twenty-four-hour collection and is unremarkable except for the distinct increase in alpha-amino nitrogen, and minimal elevation of ammonia nitrogen.

TABLE III
PLASMA CONCENTRATION OF FREE AMINO ACIDS

Amino Acids	Patient Concentration (mg. %)	Normal Concentration (mg. %) [36]
Alanine	1.28	3.01–3.73
Arginine	1.33	1.22–1.91
Asparagine + glutamine	6.70	Approx. 6.30–10.30
Citrulline	0.62	...
Cystine	1.35	1.08–1.30
Glutamic acid	1.10	0.43–1.15
Glycine	1.31	1.34–1.73
Histidine	0.77	0.79–1.48
Isoleucine	0.65	0.69–1.28
Leucine	1.03	1.42–2.30
Lysine	2.10	2.51–3.02
Methionine	0.23	0.33–0.43
Ornithine	0.48	0.62–0.80
Phenylalanine	0.67	0.69–0.95
Proline	1.05	2.01–3.34
Serine	1.35	1.01–1.25
Taurine	1.36	0.41–0.82
Threonine	1.19	1.21–1.72
Tyrosine	0.78	0.81–1.45
Valine	1.58	2.37–3.71

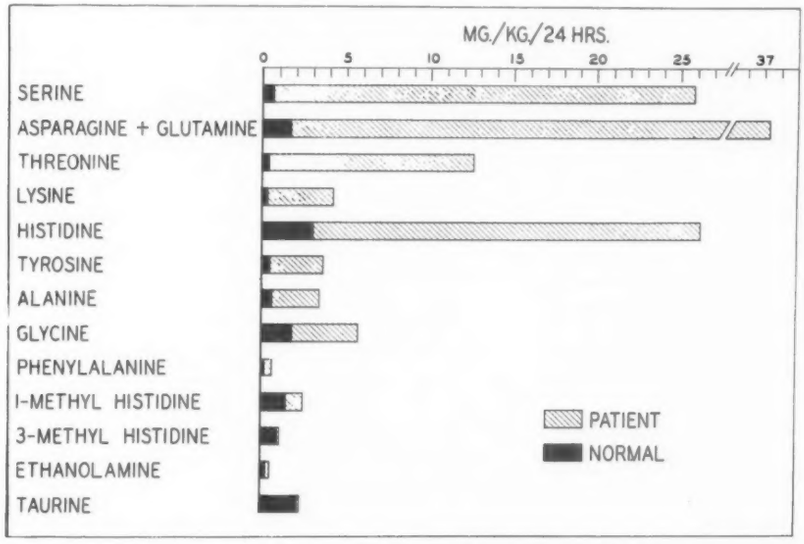


FIG. 1. Histogram comparing twenty-four hour free amino acid excretion in propositus with values for normal adults, (average normal excretion from Stein [*37*]).

Amino Acid Metabolism. Amino acid concentration in plasma and urine: The concentration of free amino acids in plasma and twenty-four hour urine specimens was recorded in the initial report. However, the values more recently obtained by a newer chromatographic method are slightly different and will therefore be summarized. Plasma concentrations (Table III) of proline, alanine, valine, lysine and leucine were distinctly below normal. Taurine concentration remained slightly elevated, while all other amino acids were present in near-normal concentrations.

The twenty-four hour urinary excretion of individual free amino acids was determined in six-day pooled, frozen specimens after adjustment to pH 2. Six observations over a three-month period with the patient on a constant diet gave strikingly similar results, which are summarized in Figure 1. As previously reported, serine, threonine, lysine, histidine and tyrosine were excreted in seven- to forty-threefold excess when compared to normal values (expressed as milligrams per kilogram per twenty-four hours to correct for the growth abnormality in our patient). In addition, all recent samples have shown excesses of asparagine and glutamine not previously noted. Although we have been unable to separate quantitatively the last mentioned compounds because of a common chromatographic peak, paper chromatography has suggested about equal concentrations of asparagine and glutamine. Alanine, glycine and phenylalanine remain in excess (three to six times normal) while excretion of taurine, 1-methyl histidine and 3-methyl histidine is probably normal. Small quantities of ethanolamine have also been observed, but leucine, isoleucine, methionine, valine, tryptophane and aspartic acid have appeared only in trace amounts.

Renal clearance of amino acids: Simultaneous inulin, creatinine and endogenous amino acid renal clearances were performed during the constant intravenous infusion of inulin. The urine was collected through an indwelling Foley catheter with distilled water and air wash-outs. Thirty minute clearance periods were used. Arterial blood samples were obtained at the mid-point of each collection period. As shown in Table IV, markedly increased clearances (five to twenty-five times normal) were noted for threonine, serine, glutamine-asparagine, histidine, tyrosine and alanine when compared with the normal clearance values recently reported by Cusworth and Dent [*11*]. Lysine, glycine, taurine and phenylalanine clearances were only moderately increased (two to fourfold). C amino acid:C inulin ratios are also reported in Table IV and denote the per cent of the filtered load of each amino acid which was excreted. These figures show that 33 per cent of filtered histidine, 17 per cent of serine, and 11 per cent of threonine were excreted, compared with estimated normal values of 6, 2 and 0.9 per cent, respectively.

TABLE IV

ENDOGENOUS RENAL CLEARANCE OF AMINO ACIDS

Amino Acid	Renal Clearance (cc./min./1.73 M^2.)		$C_{Amino\ Acid/C\ Inulin} \times 100$	
	Patient	Normal [11]	Patient	Normal*
Serine	44.4	2.5	17.3	2.0
Glutamine + asparagine	34.5	0.9	13.4	Approx. 1.8
Threonine	28.1	1.1	11.0	0.9
Lysine	3.4	1.0	1.3	0.8
Histidine	84.2	7.2	32.8	6.0
Tyrosine	12.6	1.5	4.9	1.2
Alanine	3.2	0.6	1.2	0.5
Glycine	11.9	4.2	4.6	3.6
Phenylalanine	2.7	1.1	1.0	0.9
Taurine	14.9	8.0	5.8	6.7

* Values derived from data of Cusworth and Dent [11].

Effect of food intake on amino acid excretion: In an attempt to understand the pathologic physiology of the renal tubular defect for amino acid reabsorption, the effect of alternate periods of food intake and food deprivation was studied.

Eckhardt and Davidson [12] studied the amino-nitrogen excretion in healthy adult men receiving a diet containing varying amounts of protein. When protein intake was reduced from 70 gm. to 0 gm. per day, the amino nitrogen fell about 40 per cent (from 118 mg. to 63 mg. per 24 hours). Corresponding experiments were performed by Huisman [13] in children. At three different levels of protein intake (0.38, 1.87 and 5.17 gm. per kg. per day) the amino-nitrogen excretion was found to be about 2 mg., 2.6 mg. and 3 to 4 mg. per kg. body weight per day, respectively.

To evaluate the effects of food deprivation under the conditions of our environment, two normal young adult men were studied as follows: each was maintained on a diet composed of 1.1 gm. of protein per kilogram body weight per day for seven days, after which all food was withdrawn for twenty-four hours. Twenty-four hour urine samples were collected on two successive days during the "feeding and fasting" portions of the study and the urinary alpha-amino nitrogen was determined. In both cases the excretion of alpha-amino nitrogen dropped 28 to 30 per cent during the fasting day. These data were compatible with the previously reported studies and we therefore elected to study our twelve year old propositus in a similar way. During a twenty-four hour period in which a diet composed of 2.5 gm. protein and 80 calories per kilogram body weight per day was ingested, the urinary excretion of alpha-amino nitrogen totaled 296 mg. The patient then fasted for twenty-four hours (except for water), during which time his urinary alpha-amino nitrogen dropped to 64 mg. per twenty-four hours, a reduction of 78 per cent from the previous day. We then repeated the study, collecting urine in

TABLE V

EFFECT OF FOOD INGESTION AND FASTING ON URINARY EXCRETION OF ALPHA-AMINO NITROGEN

Day of Study	Time of Collection and Amount Excreted (mg.)				24 Hours Excretion (mg.)
	6 A.M.–12 Noon	12 Noon–6 P.M.	6 P.M.–12 Midnight	12 Midnight–6 A.M.	
Feeding	54.3	141.3	218.4	26.0	440.0
Fasting	45.1	28.1	34.6	21.7	129.5

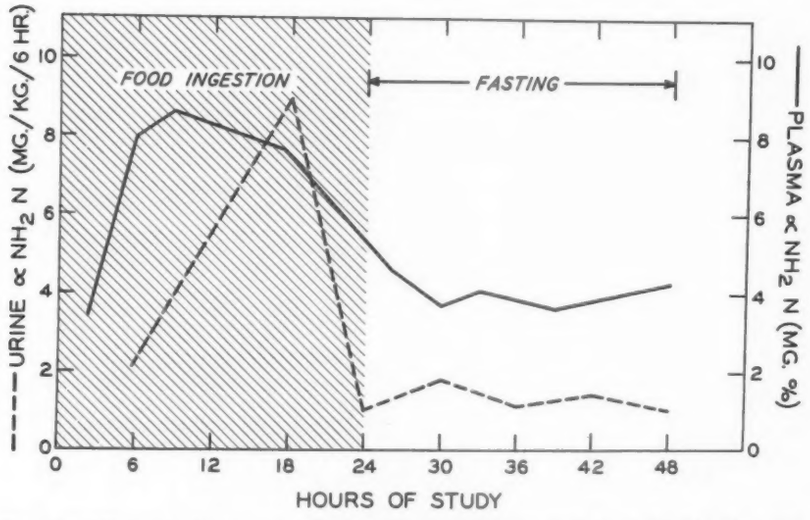


FIG. 2. Effect of alternate periods of food ingestion and food deprivation on plasma and urinary alpha-amino nitrogen concentration.

six-hour pools and following plasma alpha-amino nitrogen concentration serially throughout the forty-eight hour test period. Table v summarizes the results obtained. The drop in twenty-four hour urinary excretion of alpha-amino nitrogen was 72 per cent, confirming the magnitude of the change observed during the previous study. It should be noted that the steepest decline in the urinary excretion of alpha-amino nitrogen occurred within the first six-hour period after stopping food ingestion. Figure 2 relates plasma and urine alpha-amino nitrogen concentrations during the forty-eight hour study. During the "feeding" day, the plasma concentration of alpha-amino nitrogen rose markedly following food ingestion, concomitant with the high urinary excretion already noted. However, throughout the day of fasting, plasma concentration of alpha-amino nitrogen remained near the normal fasting value, as the urinary excretion dropped and remained constant.

Using the previously observed glomerular filtration rate we then calculated the filtered load and renal clearance of alpha-amino nitrogen during the peak excretion period of day 1 and compared these results with corresponding values on day 2. The filtered load of alpha-amino nitrogen dropped slightly more than 50 per cent with fasting while the renal clearance declined nearly 80 per cent during the same time interval. These findings suggest that food ingestion, with resultant increase in plasma amino acid concentration and renal filtered load, is followed by excessive losses of amino acids in the urine, because the defect in tubular reabsorption of amino acids prevents the enhanced tubular reabsorption which normally follows an increased filtered load. However, it should be noted that the excretion of alpha-amino nitrogen on the "fasting" day was about two to three times normal, indicating that the persistent increase in urinary loss of amino acids cannot be attributed to food intake alone, particularly in the presence of abnormal fasting endogenous amino acid clearances.

Metabolic balance and amino acid supplementation studies: The large urinary losses of several amino acids, including three "essential" ones (threonine, lysine and phenylalanine), prompted the following question: are the abnormalities in growth and muscle formation directly related to deficient quantities of amino acids needed for normal protein synthesis? An attempt was made to answer this question utilizing the metabolic balance technic. During the previously reported balance study [*7*] the patient was given a diet composed of 4 gm. of protein and 100 calories per kilogram body weight per day, and was observed to be in slightly positive nitrogen balance with a progressive weight gain of about 60 gm. per day during a twenty-four day study. Oral supplements of 1 gm. threonine and 0.5 gm. lysine per day were then added to the diet and a small but significant increase in nitrogen retention was observed; this was accompanied by distinct improvement in appetite. However, no change in rate of weight gain was noted. The dietary protein was then reduced to a

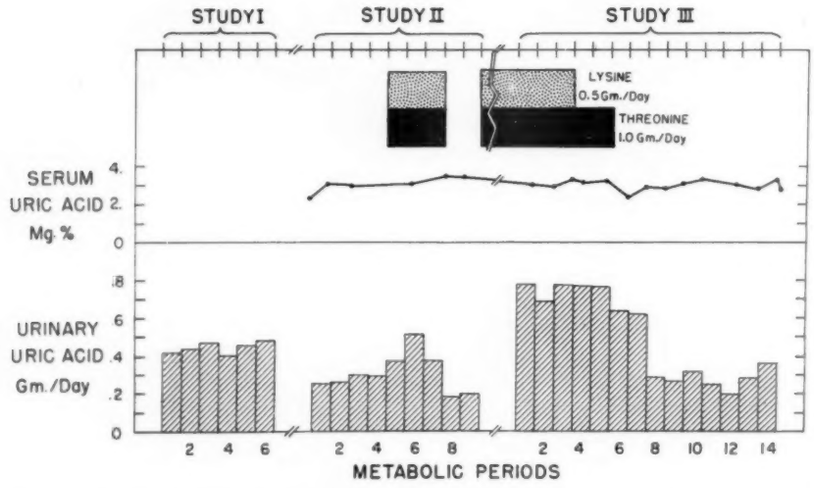


FIG. 3. Effect of threonine supplementation on plasma and urinary uric acid concentration.

more conventional intake of 2.5 gm. per kg. per day, and again nitrogen retention and slow weight gain were observed. During repeated supplementation studies with threonine (1 gm. per day) and lysine (0.5 gm. per day), threonine (1 gm. per day) alone, and the combination of histidine (4 gm. per day), serine (3 gm. per day) and threonine (2 gm. per day), the beneficial effect on nitrogen retention previously noted was not reproduced nor have significant changes in weight gain, amino acid excretion or muscle development been observed. However, when the patient was allowed to eat an *ad libitum* diet, his food intake fell to 2 gm. protein and 60 calories per kg. per day and his body weight was noted to decrease by about 40 gm. per day until the intake was increased. These findings fail to substantiate any direct relationship between aminoaciduria and growth failure, and indicate that nitrogen retention and weight gain can occur when proper nutrition is provided The data also suggest that the failure to grow is related, at least in part, to inadequate food intake when the patient is not in the controlled environment of the hospital.

Effect of Threonine on Uric Acid Excretion. During threonine supplementation studies, significant increases in the urinary excretion of uric acid were observed, as shown in Figure 3. These increases persisted after withdrawal of lysine supplements, and uric acid excretion did not return to normal until the threonine was withdrawn. Serum uric acid concentrations were unchanged during the periods of increased urinary loss. The basis for this observation is not entirely clear. A direct uricosuric effect of threonine has not been reported, and seems unlikely in view of the unchanged serum concentration. Increased uric acid excretion has been reported following ingestion of glycine [*15,16*], alanine [*15,16*], aspartic acid [*15*], glutamic acid [*15,16*], asparagine [*15*], ammonium salts [*17*], and protein supplements [*14,18*], presumably due to increased uric acid production following administration of these nitrogen sources. A similar mechanism for the threonine effect seems likely, particularly in the presence of a known chemical pathway for conversion of threonine to glycine [*19,20*].

Family Study and Genealogic Survey. Because of the familial nature of the muscle weakness, dwarfism and cor pulmonale, further study of the immediate family and close relatives was undertaken. The father, mother, twenty year old brother, six year old brother and fifteen year old half-sister were interviewed and examined. We were unable to elicit any history suggestive of consanguinity. Genetic blood grouping was performed on each member of the immediate family and no incompatible groupings were uncovered.* Growth disturbance, muscle wasting or evidence of cardiopulmonary dysfunction were uniformally absent. Chest roentgenograms of each were entirely within normal limits. Twenty-four hour urine collections were obtained from each member of the immediate family and the results will be discussed subsequently.

All living grandparents, uncles, aunts and

* These determinations were kindly performed by the Blood Bank Section of the Division of Biologic Standards.

TABLE VI

TWENTY-FOUR HOUR URINARY AMINO ACID EXCRETION IN FAMILY OF PROPOSITUS

Family Member	Proposita	Father	Mother	Brother	Brother	Half-sister	Paternal Grandfather	Paternal Aunt	Paternal-Maternal Cousin	Maternal Grandmother	Maternal Great-Aunt	Maternal Uncle	Maternal Uncle	Materna Cousin
Sex	M	M	F	M	M	F	M	F	F	F	F	M	M	F
Age (yr.)	12	41	38	20	6	15	76	35	12	61	63	37	26	3
Weight (kg.)	25.0	69.1	57.3	79.5	24.0	53.2	57.3	57.3	66.8	45.4	56.3	57.3	72.7	13.4
Urinary α-NH_2-N (mg./24 hr.)	325	142	123	454	391	131	155	142	207	138	100	102	262	53
Free amino acids in urine (mg./24 hr.)														
Taurine (86–294)*	57.9	64.4	170.4	98.0	44.9	128.8	64.8	105.3	310.1	63.6	71.1	28.0	145.4	11.8†
Threonine (15–53)	315.3	25.4	25.2	186.0	313.7	30.7	23.5	27.3	61.7	25.4	19.0	17.0	133.5	11.7
Serine (27–73)	645.4	52.3	35.9	374.5	794.9	75.4	44.6	40.9	132.7	51.5	40.2	26.9	184.8	21.2
Asparagine + Glutamine (34–92)	928.5	98.1	94.8	673.3	1299.1	157.7	91.8	76.4	226.9	106.7	82.2	82.1	417.9	56.2
Glutamic acid (<10)	<10	...	...	...	21.8	...	<10	...	...	...	...	...	<10	...
Citrulline	17.6	<10	...	...	41.5	<10	...	...	...	...	...	<10	<10	<10
Glycine (68–199)	142.9	148.6	92.4	421.6	114.6	158.1	82.9	338.1	555.4	160.1	122.5	67.6	147.5	38.8
Alanine (21–71)	85.4	25.5	38.4	131.4	199.6	33.4	31.4	19.0	87.3	31.4	26.1	10.3	68.9	18.4
Valine (<10)	<10	<10	<10	<10	57.5	<10	<10	<10	<10	<10	<10	<10	<10	<10
Methionine (<10)	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Isoleucine (12–28)	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Leucine (9–24)	<10	<10	<10	<10	12.6	<10	<10	<10	<10	<10	<10	<10	<10	<10
Tyrosine (15–49)	90.4	27.9	33.6	75.6	82.4	32.4	27.7	15.8	58.5	30.1	18.5	21.6	78.2	13.3
Phenylalanine (9–31)	15.6	18.4	18.0	23.6	42.1	18.5	13.8	10.6	20.7	15.7	11.8	13.6	17.4	<10
β-Alanine	...	<10	22.8	...	...	13.5	45.9	45.0	...	...	<10	10.0	14.0	<10
Ethanolamine	12.1	23.5	24.9	23.6	<10	30.8	25.5	15.7	38.5	21.0	18.5	16.2	22.4	<10
Lysine (7–48)	104.1	26.4	57.3	31.0	120.1	95.8	11.0	11.5	99.3	21.1	20.1	16.7	70.3	<10
l-Methyl Histidine (20–150)	63.3	40.0	14.2	133.9	200.6	31.5	27.0	32.2	106.2	44.3	50.3	<10	47.0	<10
Histidine (113–320)	654.9	90.4	159.8	581.6	670.6	228.5	66.7	55.0	313.3	121.7	123.8	76.0	501.7	86.7
3-Methyl Histidine (20–150)	25.7	67.2	54.0	75.6	<10	55.0	29.8	25.6	94.1	47.0	33.3	22.1	55.7	<10

NOTE: Aspartic acid, proline, cystine, tryptophane, arginine, and β-aminoisobutyric acid were not observed in measurable amounts in any member of the study.
* Normal range of excretion for adults (milligrams per twenty-four hours) from Stein, W. H. [37].
† Normal values for three year old child from Snyderman, S. E. [38] and Schoen, E. J. [39].

first cousins of the patient were found to live in or near a large eastern city. Personal interviews with each member of this group failed to disclose direct or indirect evidence of consanguinity. Questioning also failed to uncover any history of a disease process even remotely similar to that observed in the propositus or his deceased sibs, and no clinical features suggesting the disorder were found. We obtained twenty-four hour urine collections from each person interviewed.

Table VI is a tabulation of the data collected during the genealogic survey just mentioned. Distinctly elevated twenty-four hour urinary alpha-amino nitrogen concentrations were found in the twenty year old brother of the propositus, the six year old brother, a twenty-six year old maternal uncle, a three year old maternal female cousin, and, of unique interest, in a twelve year old female cousin, the child of a paternal aunt and a maternal uncle. Column chromatographic analysis of all urine samples was performed and corroborated the pathologic aminoaciduria in each case. The pattern of aminoaciduria in all cases was distinctly similar to that seen in the propositus, the most striking abnormalities being observed for threonine, serine, asparagine-glutamine, lysine, histidine and tyrosine. It is of particular interest that the fifteen year old half-sister of the propositus excreted distinct excesses of glutamine-asparagine and lysine despite normal twenty-four hour alpha-amino nitrogen excretion and normal quantities of the other free amino acids.

The genetic table, shown in Figure 4, sum-

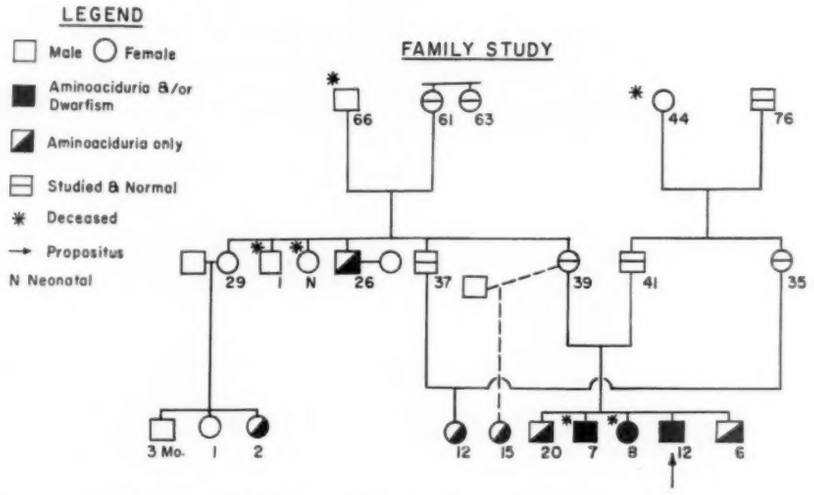


FIG. 4. Results of genealogic survey describing mode of transmission of aminoaciduria and dwarfism. See text for discussion of data.

marizes our data to date. The population sample is too small to be conclusive, but suggests the following possible explanations of the findings: (1) that the aminoaciduria and dwarfism are expressions of a single genetic abnormality transmitted as a dominant through the maternal side of the family—variable penetrance and expressivity providing a possible explanation for the phenotypic differences observed; or (2) that the aminoaciduria and dwarfism are separate genetically transmitted traits which have made themselves apparent in the sibship of the propositus. In this explanation the aminoaciduria would again appear to be a dominant while the trait for dwarfism would be considered an autosomal recessive, not apparent except in the homozygous state. At present we have no data which would allow us to distinguish between these possibilities. The presence of aminoaciduria in the half-sister lends strong support to the concept of dominant maternal transmission of the trait for this renal tubular dysfunction, but does not answer the remaining questions posed.

COMMENTS

In the original description of the abnormalities noted in this twelve year old white boy the combination of aminoaciduria and normal or low plasma concentrations of the amino acids in question suggested a defect in renal tubular function as the basis for the abnormality. The finding of significantly increased fasting endogenous renal clearances for all amino acids excreted in excess, again in the presence of normal or depressed plasma values, confirms the "renal" basis for the aminoaciduria, as originally described by Dent [*21*]. The abnormal urinary amino acid patterns exhibited by several members of the patient's family also are ascribable to faulty tubular reabsorption of amino acids. As has previously been stated [*1*], the absence of proteinuria, glycosuria or phosphaturia suggests an isolated defect in renal tubular function. This thesis has been strengthened by the absence of significant abnormalities in urinary excretion of total titratable acid, ammonia or organic acids.

The high glomerular filtration rate (when the correction for surface area is made) is difficult to explain. The absolute inulin clearance of 144 cc. per minute is much closer to normal adult values and suggests that the customary correction for body surface area may be invalid in dwarfed subjects.

It has been made increasingly clear that faulty proximal renal tubular function may result in a wide spectrum of clinical and laboratory manifestations. Numerous examples of combined glycosuria, aminoaciduria and phosphaturia have been observed (de Toni-Fanconi syndrome [*22,23*], Lowe's syndrome [*24*], heavy metal intoxication [*25,26*], maleic acid infusions in rats [*27*] and the familial syndrome described by Luder and Sheldon [*28*]). In addition more isolated defects for one or more of the substances normally reabsorbed in the proximal tubule have been reported (renal glycosuria

[*29*], hypophosphatemic rickets with glycosuria [*30*], cystinuria [*31*], glycinuria [*32*], Wilson's disease [*33*], galactosemia [*34*] and the present report). It seems likely that many discrete enzyme systems are active in proximal tubular function, and may be damaged singly or in groups, depending on the inciting cause.

We have been unsuccessful to date in relating the growth disturbance to the renal defect in amino acid reabsorption. Despite the magnitude of the defect, it is significant that at least 70 per cent of the filtered load of each amino acid is reabsorbed, and that the patient is able to maintain essentially normal plasma concentrations of the amino acids lost in largest quantity in the urine. It is possible that the aminoaciduria, by altering the total body pool of amino acids or by changing the plasma and/or tissue ratio of the individual amino acids needed for normal protein synthesis, is indeed responsible for the apparent inability of this patient to grow normally, but there is no precedent for such a thesis. This explanation seems even more unlikely when one compares the propositus, dwarfed and weak, with his six year old brother, well developed and strong, both of whom excrete essentially the same amino acids in equal quantities. These findings suggest that if the growth disturbance is not due to the cardiopulmonary abnormalities and/or the poor food intake alluded to previously, it may be related to another metabolic defect as yet undescribed. It is intriguing to postulate a defect in amino acid incorporation into protein as well as the known renal tubular reabsorptive defect to explain the growth arrest, but no evidence for such a lesion has been collected to date.

Dietary supplementation with amino acids has not proved of value in this case, despite the promising early results. The concept of supplementing a diet absolutely or relatively deficient in one or more amino acids is well established [*35*], but the use of amino acid supplements in cases similar to the one described herein has not previously been recorded. Our data suggest that the pattern of urinary excretion of amino acids, even in pathologic amounts, cannot be used as the basis for planning a therapeutic program, and may actually be of little pathophysiologic significance.

The finding of aminoaciduria in several members of the immediate family and close relatives confirm the suggestion that the pattern of amino acid excretion is a very useful "genetic marker." It seems very likely that future genetic surveys and population studies will utilize the urinary amino acid pattern much more extensively than in the past. Simple methods for two-dimensional paper chromatography are now available and should provide the geneticist with another laboratory tool to be used in conjunction with blood group analysis, hemoglobin electrophoresis, serum protein electrophoretic patterns and other serologic data.

SUMMARY AND CONCLUSIONS

Detailed evaluation of renal function in the twelve year old propositus of a familial disorder characterized by growth disturbance, aminoaciduria and hypoplastic muscle development revealed markedly increased renal clearances for the amino acids excreted in excess, thus confirming the renal etiology of the aminoaciduria. No other abnormality in renal function was found, with the possible exception of a high glomerular filtration rate.

Evidence is presented which suggests that the growth disturbance is not causally related to the aminoaciduria, but may be due to the combination of inadequate food intake, cardiopulmonary abnormalities, and perhaps a defect in protein synthesis.

Family and genealogic study has shown distinct aminoaciduria in apparently healthy members of the immediate family, unassociated with other stigmata of the disorder.

The basic questions of etiology, pathogenesis and effective therapy of this disorder remain unanswered.

ADDENDUM

On June 27, 1960, the twelve year old propositus of this study was readmitted to the Clinical Center of the National Institutes of Health complaining of cough, dyspnea and orthopnea of seven days' duration. Physical findings were unchanged from previous examinations except for the appearance of cyanosis, distended neck veins, hepatomegaly and peripheral edema. A venous pressure of 160 mm. of water (when supine) confirmed the clinical impression of right-sided congestive heart failure, superimposed on the long-standing cor pulmonale. He was placed on a combined cardiopulmonary regimen including digitoxin, salt restriction, mercuhydrin, chlorothiozide, Diamox,® expectorants and respiratory assistance with the Bennett respirator. He failed to respond to this

program or to the addition of aldosterone inhibitors and progesterone. His condition slowly deteriorated, and terminally he exhibited marked somnolence, anasarca and lethargy. He died quietly on August 26, 1960.

Postmortem examination was performed twelve hours after death and revealed the following significant findings: marked right ventricular hypertrophy and dilatation without other intracardiac abnormalities; intimal thickening, medial degenerative changes and atheromatous changes in the main pulmonary artery; passive congestion of lungs, liver, spleen and kidneys; no other gross or microscopic renal disease; and, of greatest interest, diffuse changes in the skeletal musculature consisting of fatty infiltration, loss of cross striation, increased collagen content, foci of flocculation, and abortive attempts at regeneration in some large and medium-sized muscle fibers. Dr. Milton Shy of the National Institute of Neurological Diseases and Blindness reviewed the muscle histopathology, and was of the opinion that the changes were compatible with a definite, but non-specific primary myopathic lesion.

The intriguing possibility of a relationship between the abnormal amino acid metabolism and the pathologic condition of muscle still remains, but more evidence is needed to clarify this important point.

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Diabetic Glomerulosclerosis*

A Long-Term Follow-Up Study Based on Renal Biopsies

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IT has been twenty-four years since Kimmelstiel and Wilson first described what is now generally recognized to be a specific renal lesion seen only in diabetes mellitus [*1*]. During these years a rather voluminous literature has appeared [*2–4*] concerning the etiology, pathogenesis, specificity and significance of this lesion, which they termed intercapillary glomerulosclerosis. The clinical manifestations of the Kimmelstiel-Wilson syndrome (diabetes, renal disease, edema, proteinuria and hypertension) were first thought to be highly suggestive of the pathologic lesion [*5,6*], and then rejected as non-specific for intercapillary glomerulosclerosis [*7,8*].

The majority of the earlier series of cases [*3,4,9–11*] referred exclusively to the nodular lesion originally described by Kimmelstiel and Wilson. In 1944 Laipply et al. [*8*] described another glomerular lesion, diffuse rather than nodular in character, which was also considered to be specific for diabetes. This lesion was not accepted as an entity by most observers and still remains a source of controversy. In 1953 Bell [*2*] set forth specific criteria for the recognition of the diffuse lesion, which he considered was readily distinguishable from chronic glomerulonephritis and nephrosclerosis despite their several common features.

On reviewing the renal biopsies in diabetic patients performed by our group in the last nine years, several of the patients were found to have had the nephrotic syndrome at the time of biopsy. Clinically they were thought to have diabetic glomerulosclerosis; but the pathologic diagnosis was nephrosclerosis, a lesion which is not associated with the nephrotic syndrome. On re-examining these biopsy specimens and applying Bell's criteria, the diffuse lesion was seen in every instance. Lambie and MacFarlane in 1955 [*12*] and more recently Gellman et al. [*13*] have also presented evidence for the occurrence of two renal glomerular lesions in association with diabetes mellitus. There is less agreement about the relationship between them. Since the exact location in the glomerulus of both the diffuse and nodular lesions remains unsettled, and since the diffuse involvement was not mentioned in Kimmelstiel and Wilson's original article, it would seem more appropriate to refer to either type of abnormality as diabetic glomerulosclerosis (DGS) rather than as intercapillary glomerulosclerosis or the Kimmelstiel-Wilson lesion.

MATERIALS AND METHODS

Prior to the development of the technic for performing renal biopsies, all of the reported series of DGS were based on autopsy material. In 1953 two of us (A. E. P. and J. S. H.) published the first series of needle biopsies of the kidney performed in the United States [*14*]. In this series of fifty biopsies dating back to November 1951, seven cases were included which later proved to be DGS. Since that time sixty-four biopsies have been performed in fifty-seven diabetic patients, all of whom had some clinical evidence of renal disease. (Table 1.) Of this number, ten biopsies were inadequate for definitive diagnosis. Six patients (seven biopsies) were found to have renal disease other than DGS. In forty-one patients with forty-seven biopsies a diagnosis of DGS was made. Thirty-two of

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TABLE I
RENAL BIOPSIES IN DIABETIC SUBJECTS

Diabetic Patients	No. of Patients	No. of Biopsies
Total	57	64
With DGS	41	47
Without DGS	6	7
Biopsies inadequate	10	...

these biopsies were performed because of the clinical impression of possible DGS. The remaining fifteen biopsies were obtained without strong clinical evidence of DGS but with diagnoses of other forms of renal disease before biopsy.

Three patients had more than one biopsy; one patient had two biopsies, one patient had three, and one patient had four biopsies during this period of time. The length of follow-up has varied from seven days to eight years. Of the forty-one patients with biopsy evidence of DGS, twenty-four (58.5 per cent) had diffuse lesions and seventeen (41.5 per cent) had the nodular as well as the diffuse lesion. Twenty-five patients have died. Eleven of these had the diffuse form and fourteen had the nodular form of DGS. Autopsy was performed in five patients with the diffuse lesion and in seven patients with the nodular lesions. In fifteen patients the pathologic process was reevaluated by subsequent biopsies or at autopsy. (Table II.)

Needle biopsy of the kidney was performed by the method previously described by Parrish and Howe [*14*]. Each of the biopsy and autopsy specimens was stained with hematoxylin and eosin, periodic acid-Schiff, Alcian Blue and Wilder's silver reticulum stains. The slides were then graded from 0 to 4 plus for each of the following: arteriolar hyalinization, exudate, "clumping," diffuse involvement, nodular involvement, interstitial fibrosis and interstitial inflammation. The special stains (periodic acid-Schiff, Alcian Blue and silver) were also graded from 0 to 4 plus for each of these entities. Particular attention was paid to patients with serial biopsies or with biopsy and autopsy.

Finally, the histologic appearance was correlated with the clinical and laboratory data in an attempt to determine which of the clinical features were most helpful in making the diagnosis of DGS.

RESULTS

Pathology. The glomerular lesion: The nodular lesion of DGS is now commonly recognized and generally accepted as being pathognomonic of diabetes mellitus. It is a rounded hyaline body of variable size, occurring as single or multiple masses in the periphery of one or more glomeruli.

TABLE II
RENAL BIOPSIES IN PATIENTS WITH DIABETIC GLOMERULOSCLEROSIS

Data	No. of Patients		
	Diffuse Lesion	Mixed Lesion	Total
Patients	24 (58.5%)	17 (41.5%)	41
Biopsies	29	18	47
Deaths	11 (45.8%)	14 (82.4%)	25
Autopsies	5	7	12
Repeat biopsy or autopsy	7	8	15

Several nuclei may be present in the periphery of the nodule but not at its center, and it is frequently surrounded by a patent or dilated capillary loop. The nodule stains with eosin, periodic acid-Schiff and silver stains; the latter often brings out within the nodule a concentrically laminated arrangement of the hyaline material. It stains very faintly or not at all with Alcian Blue and colloidal iron.

The diffuse lesion has proved to be a source of considerable confusion because of its similarity to other types of glomerular sclerosis, particularly that due to arteriolar nephrosclerosis. Bell's histologic criteria [*2*] for the identification of the diffuse form of DGS are as follows: (1) hyalinization of arterioles, afferent and efferent; (2) diffuse thickening and hyalinization of the intercapillary septums; and (3) disappearance of the inner basement membranes. We are in complete agreement with these criteria as far as light microscopy is concerned, and have used them in the histologic diagnosis of our renal biopsy specimens. Some additional criteria which we have found helpful in confirming the diagnosis are: (4) "clumping" of hyaline deposits; (5) persistence of large glomeruli; (6) patency of capillaries until the late stage; and (7) unchanged or increased numbers of epithelial cell nuclei in the hyaline material.

Histochemical characteristics of the glomerular lesion: The hyaline material deposited in the glomeruli in both the nodular and diffuse lesions stains with acidophilic stains such as eosin; it is positive to the periodic acid-Schiff reaction; it reduces silver, although with variable intensity; it does not stain with Alcian Blue or with Hale's

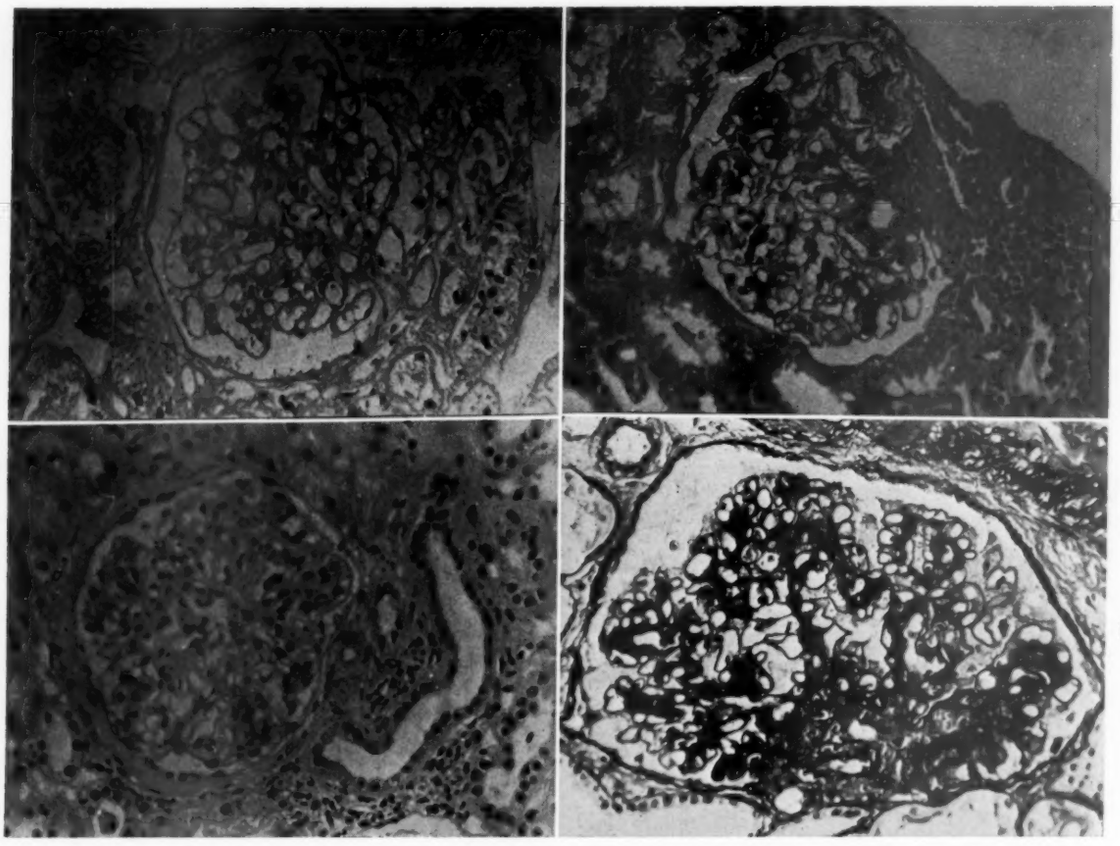


FIG. 1A–D. A, glomerulus showing early focal hyaline deposits of diffuse DGS. B, the same patient, one year later. Hyaline deposits are more extensive. C, biopsy specimen of the same patient three years later shows involvement of the entire glomerulus by confluent hyaline material. Clinically, this patient has mild azotemia, proteinuria and lipiduria as the only manifestations of renal disease. D, moderately extensive focal hyaline deposits (periodic acid-Schiff stain). Note that the glomerulus remains large, and that the capillaries are open.

colloidal iron; it is not removed by digestion with diastase. These reactions seem to characterize the substance as a neutral polysaccharide. It is definitely not glycogen and contains little or no acid mucopolysaccharides. Unfortunately, most of these histochemical reactions are shared by the glomerular basement membrane as well as by the hyalinized arterioles. Therefore, the stains and histochemical reactions used have not established whether the glomerular lesion represents focal thickening of the basement membrane or intercapillary deposits of acellular material. The Alcian Blue stain, specific for acid mucopolysaccharides [*15*], stains the normal basement membrane of the glomerulus but not the epithelial cells. The hyaline deposits of DGS also fail to stain with Alcian Blue, in this respect resembling the epithelial cells rather than the basement membrane.

Hyalinization of arterioles: Bell has stressed the frequency and specificity of hyalinization of the efferent arterioles in diabetes mellitus [*2*]. He considers it a useful criterion for the diagnosis of the diffuse type of DGS. We are in agreement with this view point, although we have not found it essential to distinguish between hyalinization of afferent and efferent arterioles. Hyalinization of efferent arterioles usually follows afferent arteriolar hyalinization in diabetes, and distinction between the two may be difficult and at times impossible.

In our series, all patients showed definite hyalinization of arterioles, which varied quantitatively between 1 and 4 plus. Since all biopsy specimens with the glomerular lesions of DGS showed arteriolar hyalinization even in the earliest stages, we believe that it regularly precedes the development of the glomerular lesions. It is interesting to speculate whether this represents a pre-glomerulosclerotic stage of diabetes mellitus. This question can probably be answered only by serial renal biopsies in

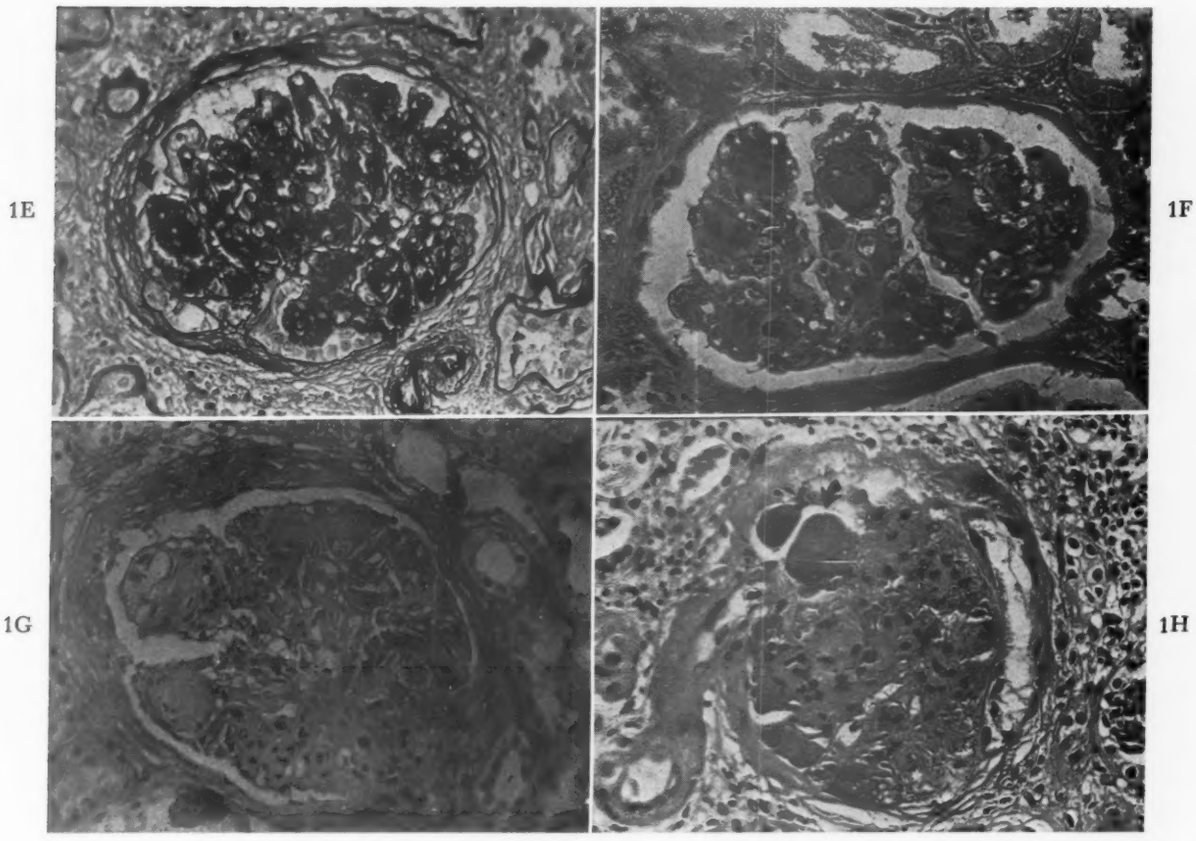


FIG. 1E–H. E, diffuse DGS, with "clumping" of hyaline material (periodic acid-Schiff stain). F, and G, mixed DGS, showing well defined nodules and diffuse hyaline involvement of the glomeruli. H, mixed DGS, with collections of exudate at the periphery of the glomerulus.

diabetic patients without evidence of renal disease.

Histogenesis of the glomerular lesion: The earliest recognizable stage of the diffuse glomerular lesion of DGS ascertainable by light microscopy consists of small focal deposits of hyaline material which appear to be located in or about the epithelial cells in the intercapillary spaces of the glomeruli. These deposits contain one or more nuclei and tend to obscure the outer border of the basement membrane. (Fig. 1A.) Subsequently, the hyaline deposits become more extensive. The glomerulus remains large, however, and the capillaries remain patent (Fig. 1B and 1D), unlike the glomerulus of chronic glomerulonephritis or benign nephrosclerosis. At this stage a frequent occurrence is the formation of small, irregular, focal hyaline lesions, an appearance which we have designated as "clumping." (Fig. 1E.) These "clumps" are decidedly smaller than the nodules, less spherical in shape, and may be located any place in the glomerulus. Bell regards these "clumps" as early forms of nodules, thus representing a transition between the diffuse and nodular forms of DGS. Our material lends no support to this interpretation. Whereas "clumping" was relatively common, occurring in thirty-two patients, subsequent biopsy or autopsy examination did not reveal the development of true nodules in any case. We must conclude that "clumping" represents a focal accumulation of hyaline material which is decidedly helpful as a histologic criterion of DGS, is commonly found in diffuse DGS, but is apparently not related to the nodular lesion.

The later stage of the diffuse glomerular lesion consists of increasing amounts of confluent hyaline material involving the entire glomerulus. (Fig. 1C.) Finally it compresses the capillaries, with the production of an avascular hyaline glomerular tuft.

The exact location of the glomerular lesion has been the subject of much debate. Kimmelstiel and Wilson [*1*], McManus [*18*], Bell [*2*] and others [*12*] have expressed the opinion that the

TABLE III
SEX AND AGE DISTRIBUTION OF FORTY-ONE PATIENTS WITH DGS

	Diffuse Lesion	Mixed Lesion	Total
Sex			
Males	20	12	32
Females	4	5	9
Age (yr.) at onset of diabetes			
Average	39.5	42.8	40.9
Range	16–75	16–61	16–75
Age (yr.) at first biopsy			
Average	48	55.6	51.3
Range	28–75	29–77	28–77
Duration of diabetes before diagnosis of DGS			
Average	8.3	12.8	10.2
Range	1 mo.–21 yr.	2–27 yr.	1 mo.–27 yr.

hyaline accumulation occurs in the intercapillary space. Allen [*19*], and more recently Gellman et al. [*13*] believe that it represents a focal thickening of the glomerular basement membrane. Recent electron microscopic studies [*16,17*] have shown thickening of the basement membrane to be one of the earliest lesions in DGS. The hyaline substance appeared to be deposited between the cell membranes of adjacent endothelial cells, and could sometimes be demonstrated to be continuous with the basement membrane.

Our studies of the very earliest diffuse lesions, their progression, and their appearance with special stains under light microscopy suggested that the hyaline deposits occurred in or about the epithelial cells in the intercapillary spaces. It may be necessary to alter this impression in view of the latest electron microscopy findings [*16,17*]. However, the fact that Alcian Blue stains the normal glomerular basement membrane, but not the epithelial cells or the hyaline deposits of DGS, suggests that the hyaline material may not be derived from the basement membrane. If it is derived from it, as has been suggested [*17*], it seems likely that it consists of deposits in the basement membrane which differ histochemically from the normal basement membrane. Whereas electron microscopy will undoubtedly provide the answer to this question, we do not believe that enough data are presently available to warrant any final conclusion.

Relationship between diffuse and nodular lesions: The relationship between the two types of lesions remains obscure. Twenty-four patients showed only the diffuse lesion; seventeen showed both the diffuse and nodular lesions. The nodular lesion was never seen alone, but only in conjunction with the diffuse lesion. (Fig. 1F and 1G.) We shall therefore refer to those patients who showed the nodular lesion as the mixed type.

In no patient have we observed the development of the mixed from the diffuse lesion. Five patients with the diffuse type of process were followed up from two to four years with biopsy and autopsy examinations; two patients were followed up from one to five years with repeated biopsies. The diffuse lesions progressed in every instance, yet no nodules were seen to develop. It is possible that more than five years are needed for the evolution of the nodules. However, we are inclined to believe that the two are separate entities.

The progression of the nodule was variable in our series. In one instance there was a definite increase in the size and number of the nodules at the time of the second biopsy four months later. Autopsy was performed from seven days to two years after biopsy in seven cases of the mixed type. Of this number, progression of the nodular lesion was evident in five.

Other lesions: The exudative lesion is not specific for DGS [*12*] and was seen in only thirteen of our patients. Similar lesions have been reported in other diabetic patients and in other conditions such as chronic glomerulonephritis [*20*]. The exudate appears as a rounded or crescent-shaped, glossy, fibrinoid-like mass situated at the periphery of the glomerular tuft. (Fig. 1H.) When seen in DGS it frequently surrounds the nodules. It is usually found in patients with the most severe degree of renal damage.

Interstitial fibrosis and inflammation ranged from entirely absent (0) to severe (4 plus). Neither of these findings showed any consistent correlation with the type or severity of the glomerular abnormality.

Clinical Correlations. The sex distribution, age at the time of first biopsy, age at the onset of diabetes, and duration of diabetes are listed in Table III. Most autopsy series have reported a large female population with DGS [*4,12,19*]; the diabetic population as a whole contains a larger percentage of females [*21*]. The predominant male population in our series reflects the fact that the majority of our patients were drawn from a Veterans Administration hospital.

Age at onset of diabetes: It is difficult to determine accurately the actual onset of diabetes, especially in the older age groups in which diabetes is frequently mild in nature and may

TABLE IV
COMPARISON OF AGE AT ONSET AND DURATION OF DIABETES BEFORE DIAGNOSIS OF DGS

Age (yr.) at Onset of Diabetes	Average Duration of Diabetes before Diagnosis of DGS (yr.)	
	Diffuse Lesion	Mixed Lesion
<20	12.3 (3)*	13.0 (1)*
21–30	11.6 (5)	19.0 (3)
31–40	8.0 (6)	18.7 (3)
41–50	6.7 (3)	10.0 (6)
51–60	6.1 (6)	7.3 (3)
>61	1 mo. (1)	2.0 (1)

* Parentheses include the number of patients in each group.

TABLE V
INCIDENCE OF THE KIMMELSTIEL-WILSON SYNDROME

	Diffuse Lesion		Mixed Lesion	
	No.	%	No.	%
Proteinuria	22	91.6	17	100
Azotemia	14	58.3	17	100
Hypertension	18	75.0	14	82.3
Edema	15	64.2	14	82.3
Patients with complete syndrome	7	29.2	12	70.6

have been present for a considerable time before detection. In our series, the average age at the onset of diabetes was very similar in patients with both the diffuse lesion and the mixed lesion. (Table III.) This age was considerably lower than the peak incidence for the onset of diabetes in the general diabetic population [*21*]. It appears that in the patient destined to show DGS, diabetes tends to develop at an earlier age than would be expected. The age at onset of diabetes does not, however, determine the type of glomerulosclerosis that will develop.

Age at time of first biopsy: The age at the time of the first renal biopsy was chosen to represent the onset of known DGS. While it is realized that the process had existed for varying periods prior to the biopsy, it represents the earliest age at which a definite diagnosis of DGS could be made without performing biopsies on a large number of diabetic patients with no evidence of renal disease. The age range at the time of biopsy is similar in the two groups but the average age showed a 7.6 year difference. (Table III.) Although the group with the mixed lesion was generally older than the group with the diffuse lesion, the mixed lesion appeared to develop at an earlier age than was generally thought in the past [*4*]. Three of our patients with mixed DGS were under fifty years of age and one was under thirty years of age. This may reflect the fact that patients with juvenile diabetes are surviving long enough to have the mixed type of glomerulosclerosis develop.

Duration of diabetes at the time of first biopsy: The duration of diabetes from onset to the time of biopsy represents a rough approximation of the time necessary to develop DGS. Even though the date of onset of diabetes was not precise, and the renal disease had been present for variable periods at the time of first biopsy, this figure is still helpful when used for purposes of comparison. The patients with mixed lesions had diabetes for a considerably longer period than those with diffuse lesions, although the difference was not as great as had been anticipated. (Table III.) Nine patients with the diffuse lesion had had diabetes for longer than nineteen years without having nodules develop, but only five of those with the mixed lesion had had diabetes for less than ten years.

There was no direct correlation between the duration of the diabetes and the severity of the glomerular lesion in either type. Others [*12,22,23*] have found a definite relationship. Laipply [*8*] and Dana [*10*], however, did not consider the duration of diabetes to be a determinant in the development of the lesion.

It was also found (Table IV) that the younger the patient was at the onset of diabetes, the longer had the diabetes been present before the biopsy diagnosis of DGS. This trend was found in both the diffuse and mixed types and would seem to suggest that a longer time was needed for the development of the lesion in the younger age groups. However, this is probably only a reflection of the more prompt diagnosis of diabetes in the juvenile patients, and does not represent a greater "resistance" on the part of the young diabetic patient to the development of glomerulosclerosis.

History of renal disease: None of our patients gave a history of unequivocal renal disease in the past. Symptoms directly referable to the urinary

TABLE VI
INCIDENCE OF ASSOCIATED VASCULAR DISEASE IN PATIENTS WITH DGS

	Diffuse Lesion		Mixed Lesion	
	No.	%	No.	%
Retinopathy				
Keith-Wagener grade				
0–1	9	37.5	2	11.8
2	5	20.8	3	17.7
3*	10	41.7	11	64.7
Myocardial infarction	2	8.3	6	35.3
Peripheral vascular disease	3	12.5	6	35.3

* Includes patients with or without microaneurysms.

tract were generally vague in nature and unreliable as to time of onset. Five patients complained of nocturia; frequency of urination was the only complaint elicited in two others; dysuria was mentioned twice. The onset of renal disease could not therefore be determined clinically with any degree of accuracy.

Presence of hypertension: The finding of hypertension (blood pressure above 140/90 mm. Hg) for our entire group was 78 per cent as compared to 61.8 per cent in one series of diabetic patients without DGS [*2*]. It was more common in patients with the mixed lesion than in those with diffuse involvement, but the difference was small. (Table v.) Patients with the mixed form of DGS tended to have a higher systolic pressure (average 192 mm. Hg) than those with the diffuse lesion (average 174 mm. Hg). Conversely, the latter had higher diastolic pressures (average, 97.4 mm. Hg) than the patients with the mixed lesion (average, 89.6 mm. Hg). The differences were not statistically significant, however, and mean arterial pressures did not vary significantly between the two groups.

Rogers and Robbins [*7*] concluded that hypertension was the most variable and least significant finding as a diagnostic aid in DGS. Hall [*4*], on the other hand, found the degree of hypertension to be roughly proportional to the degree of renal arteriolosclerosis in patients with DGS. We were unable to confirm this finding. The height of both the systolic and diastolic pressures in our patients correlated poorly with the severity of either lesion and with the degree of arteriolar hyalinization.

Associated Vascular Disease. Retinopathy: The fact that microaneurysms occur seldom anywhere but in the retinas and renal glomeruli of diabetic patients [*24*] suggests a possible relationship between them. However, they have been shown to differ morphologically [*25*]. In addition, microaneurysms have been reported in diseases other than diabetes [*26,27*], thus indicating their lack of specificity for this disease. All degrees of retinopathy were present in our patients with DGS, together with all grades of severity of the renal lesion. The extent of the retinal abnormality showed no correlation with the type or severity of the renal involvement. We are thus in agreement with Ashton [*24*] who stated that the retinopathy could precede diabetic nephropathy.

The presence of severe retinopathy (grade 3 eyegrounds with or without microaneurysms) did not appear to be related to age, since in both groups the patients with the more severe retinal involvement tended to be a little younger than average. Scott [*28*] concluded that retinopathy was related to the duration of diabetes. In our series, on the other hand, the degree of retinopathy was independent of the duration of diabetes in patients with either the diffuse or the mixed lesion.

When the two groups of patients were compared, an appreciable difference was found in the extent of their retinal involvement. (Table VI.) Whereas 37.5 per cent of the patients with the diffuse lesion had normal or grade 1 eyegrounds, only 11.8 per cent of those with the mixed lesion had normal eyegrounds. Among the patients with diffuse DGS, 41.7 per cent had grade 3 eyegrounds, while those with the mixed form included 64.7 per cent with grade 3 retinopathy. These findings are in agreement with those of Kimmelstiel and Porter [*29*] who found in a review of the literature that retinopathy was present in 86 per cent of patients with diabetic glomerulosclerosis.

Myocardial infarction and peripheral vascular disease: Both myocardial infarction and peripheral vascular disease were more frequently encountered in the patients with mixed DGS than in those with the diffuse lesion alone. (Table VI.) Whereas myocardial infarction was present in only two of the subjects with the diffuse lesion, it was found in over one-third of those with the mixed type of DGS. Similarly, peripheral vascular disease was present in three patients (12.5 per cent) with the diffuse and in six pa-

tients (35.3 per cent) with the mixed lesion. In neither group were these complications necessarily associated with the more severe degrees of renal pathology. Among the patients with diffuse DGS, both vascular complications were found only in the older patients (over fifty-five years of age), without relationship to the duration of their diabetes. In those with the mixed form there was no discernible correlation between the presence of these entities and the age or duration of diabetes.

The nephrotic syndrome: We used the term nephrotic syndrome to designate (1) proteinuria of more than 3 gm. per twenty-four hours, or 4 plus; (2) hypoalbuminemia of less than 3 gm. per 100 ml.; (3) hypercholesterolemia, or serum cholesterol above 300 mg. per 100 ml.; (4) edema; and (5) fat in the urine as determined by Sudan III stain of the urinary sediment. The complete syndrome developed in five patients. Six patients with diffuse lesions and four with mixed lesions fulfilled four of the five criteria listed. Nine patients with diffuse and eleven with mixed DGS met three of the criteria, including marked proteinuria and edema in every case. Thus, if a broad definition of the nephrotic syndrome is accepted, 37.5 per cent of the patients with diffuse lesions and 64.7 per cent of those with mixed lesions were nephrotic at some time during the course of their illness. The presence of the nephrotic syndrome correlated poorly with the severity of the diffuse lesion, and not at all with the severity of the mixed lesion.

The Kimmelstiel-Wilson syndrome: The Kimmelstiel-Wilson syndrome, as originally described, consists of diabetes, renal failure, proteinuria, hypertension and edema [*1*]. Table v shows that seven (29.2 per cent) patients with diffuse DGS and twelve (70.6 per cent) mixed lesions had the complete clinical syndrome. This represents a total of nineteen patients, or 46.3 per cent, and parallels the total number of patients who were nephrotic (twenty, or 48.8 per cent). The presence or absence of the Kimmelstiel-Wilson syndrome could not be correlated with the severity of either lesion on biopsy. Moreover, it has been reported to occur in diabetic patients without DGS [*7*]. Its usefulness as a symptom-complex in the diagnosis of DGS would seem to be no better than that of the nephrotic syndrome—a less specific term which includes DGS among its causes.

Amelioration of diabetes with the development of DGS: Zubrod [*30*] and others [*31*] have reported instances of amelioration of the diabetic state with the onset of diabetic nephropathy. Epstein [*11*] and Runyan [*32*], however, found no consistent reduction in insulin requirement in patients with the mixed lesion. We ourselves have seen a striking example of a patient with severe diabetes of fifteen years' duration who had required up to 100 units of insulin a day. After the development of DGS, as proved by renal biopsy, she went into remission and did not require any insulin for more than a year prior to her death [*33*].

TABLE VII
ACIDOSIS IN DGS

	Diffuse Lesion	Mixed Lesion
No. of patients with acidosis	10	3
Within 5 years before biopsy	7	2
At biopsy admission	4	0
After biopsy diagnosis DGS	5	1

A reduction in insulin requirement of 50 per cent or more was chosen as the criterion to indicate amelioration of diabetes in our patients. Despite the fact that other factors can result in lowering of the insulin requirement, we believed that this was the best objective evidence for "amelioration." Five of our patients had mild diabetes from the start, and were always treated with diet alone. Of the remaining thirty-six, twelve (33.3 per cent) had the requisite decrease in insulin requirement. Four of these patients had diffuse DGS and eight had mixed DGS. The decreased insulin need correlated poorly with the presence of azotemia, with the development of the nephrotic syndrome, and with the severity of the lesion on biopsy. Three of our six diabetic patients with renal diseases other than DGS also had a reduction in their insulin requirement of more than 50 per cent. This suggests that it is renal disease, rather than DGS, which accounts for the observed amelioration in the diabetic state.

Acidosis: The development of acidosis has been considered to be rare in patients with DGS [*30*]. Thirteen patients in our series had diabetic acidosis at some time in their course. Table VII shows that in the group with diffuse lesions acidosis developed more frequently than in those with mixed DGS, both before and after the biopsy diagnosis of DGS. This finding correlates

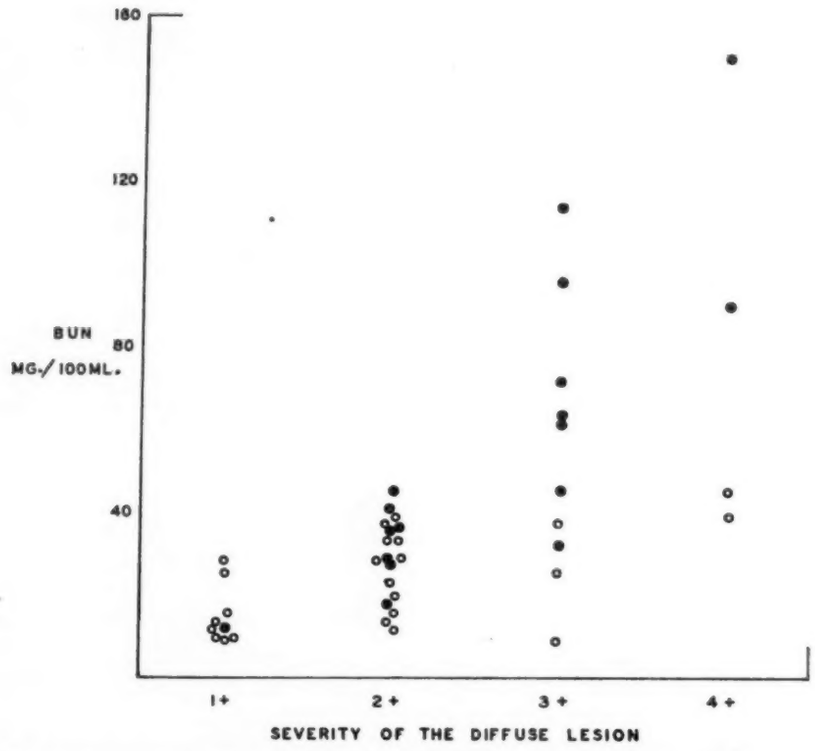


FIG. 2. Comparison of the severity of the diffuse lesion with the blood urea nitrogen levels at the time of biopsy in forty-one patients with DGS. The open circles indicate the patients with diffuse DGS. The dots refer to patients with mixed DGS.

well with the greater frequency of amelioration of diabetes in the patients with the mixed lesion.

Renal insufficiency: The degree of severity of the renal disease was compared in the patients with diffuse and mixed DGS according to (1) elevation of the blood urea nitrogen above 18 mg. per 100 ml. and (2) the presence of proteinuria. Fourteen patients (60 per cent) with the diffuse lesion had azotemia at the time of biopsy, but no blood urea nitrogen value exceeded 45 mg. per 100 ml. Values ranged from 9 to 45 mg. per 100 ml., with an average of 24 mg. per 100 ml. All the patients with the mixed lesion had azotemia, and showed considerably higher blood urea nitrogen levels on the average. The range was from 19 to 150 mg. per 100 ml., with an average of 62 mg. per 100 ml. The single patient with a slight elevation of 19 mg. per 100 ml. showed 2 plus diffuse and 1 plus nodular changes on biopsy. The remainder all had values above 28 mg. per 100 ml.

There was a good correlation between the elevation of the blood urea nitrogen and the severity of the diffuse lesion as graded on biopsy specimens. No such correlation existed with the severity of the nodular lesion. Since the nodular lesion was always accompanied by some degree of diffuse involvement, the elevation of the blood urea nitrogen was plotted against the severity of the diffuse lesion in both groups together. Figure 2 shows that it is the degree of diffuse DGS which seems to determine the degree of azotemia.

The presence of proteinuria was the most common abnormality and was consistently the earliest positive finding in our patients. It was found in twenty-one (87.5 per cent) of the patients with diffuse DGS and ranged from a trace on random urinalysis to 16 gm. per twenty-four hours. In two of these patients, it was the sole evidence of renal disease.

Proteinuria was absent at the time of biopsy in only three patients, all of whom had normal blood urea nitrogen levels. One showed minimal diffuse glomerulosclerosis and minimal arteriolar hyalinization at the first biopsy. Three subsequent biopsies over a five year period showed gradual progression of the lesion. Proteinuria was noted one year after the first biopsy, and a

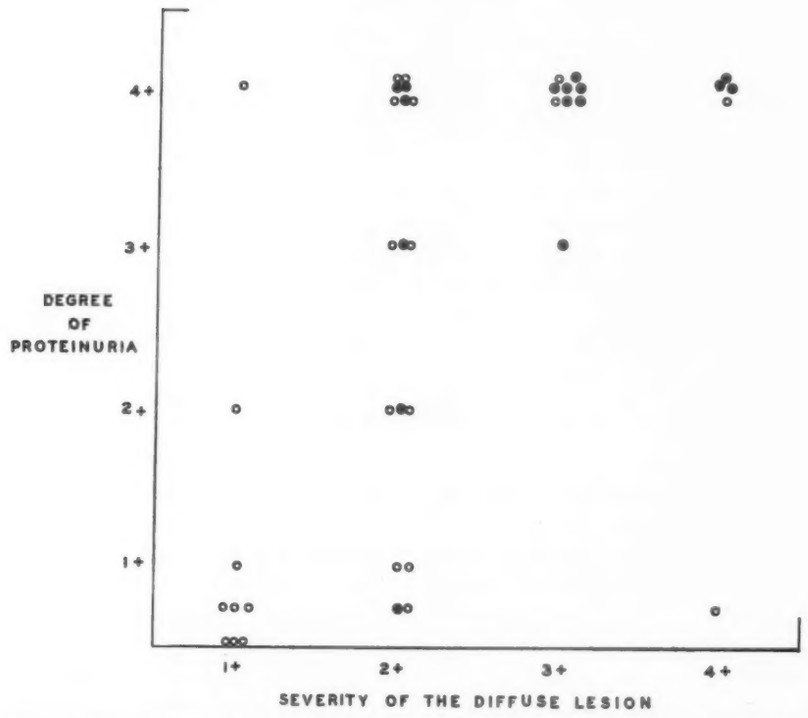


FIG. 3. Comparison of the degree of proteinuria at the time of biopsy with the severity of the diffuse lesion in twenty-four patients with diffuse DGS (open circles) and sixteen patients with mixed DGS (dots).

mild degree of azotemia appeared four years later. The second patient showed minimal diffuse DGS on biopsy. He died three years later in diabetic acidosis, and 4 plus proteinuria was recorded on his final admission. An autopsy revealed definite progression of the diffuse lesion. The third patient showed progression of diffuse DGS on repeated biopsies without the appearance of proteinuria.

All the patients with mixed DGS had proteinuria at the time of biopsy and in thirteen (76 per cent) it was of a marked degree. The severity of the proteinuria correlated poorly with the extent of nodular changes, but showed a significant relationship to the severity of the diffuse lesion in all the patients. (Fig. 3.)

Hypoproteinemia and edema: Twenty-eight of the forty-one patients studied were edematous at the time of initial biopsy. Fourteen of these had the diffuse lesion and fourteen the mixed lesion. The majority of the edematous patients were in congestive heart failure. Other causes of edema were the nephrotic syndrome (five patients) and peripheral vascular disease (two patients). In three instances the cause of the edema was not apparent. Only five of the edematous patients had hypoproteinemia (two diffuse and three mixed). The level of their hypoproteinemia could not be correlated with the severity of their lesions, nor was it associated with massive proteinuria. It may be concluded, therefore, that hypoproteinemia is not a significant feature of DGS and occurs only rarely. When it does occur, it is usually a late manifestation [*12*] and probably contributes little to the development of edema. Edema, on the other hand, is frequently seen in DGS and may be of various etiologies, the most common being congestive heart failure.

Other diabetic patients undergoing biopsy: There were six diabetic patients in the series who did not have DGS on biopsy. (Table VIII.) In five of these patients clinical symptoms developed which suggested DGS by the usual criteria. Indeed, they exhibited many of the features seen in the patients with proved DGS. However, all six patients (seven biopsies) were found to have other forms of renal disease on needle biopsy, Thus emphasizing the non-specificity of the "typical" clinical picture. Similar observations have been made in larger autopsy series of diabetic subjects who were suspected of having diabetic nephropathy during life but who had no

TABLE VIII
DIABETIC PATIENTS WITH RENAL DISEASE OTHER THAN DGS

No.	Age at Biopsy (yr.)	Duration of Diabetes (yr.)	Biopsy Diagnosis	Proteinuria	Edema	Azotemia	Blood Pressure (mm. Hg)	Drop in Insulin Need
1	51	1	Chronic GN*	3.8 gm./24 hr.	0	Yes	170/80	No
2	56	20	Nephrosclerosis	1.4 gm./24 hr.	Yes	Yes	160/100	No
3	49	4	Nephrosclerosis, pyelonephritis	2.9 gm./24 hr.	Yes	Yes	168/108	Yes
4	50	5	Membranous GN	2+	Yes	No	160/100	Yes
5	43	1	Acute GN	Trace	0	No	122/70	No
6	32	17	Chronic GN	4+	0	Yes	170/110	Yes

* GN = Glomerulonephritis.

trace of this disease at postmortem examination [*10,23,32*].

Follow-up data. Table IX shows the follow-up data for the forty-one patients included in this series. It may be seen that the average age at death of those with diffuse and mixed DGS was very similar: 52.5 and 56 years. This is in agreement with the findings in Epstein's series [*11*] in which the average age at death was fifty-five years.

The entire duration of diabetes from onset to death was almost identical in the two groups. However there was a marked difference between them in the duration of life after the diagnosis was definitely established by renal biopsy. Patients with the diffuse lesion lived an average of 2.9 years after biopsy diagnosis, whereas those with mixed DGS who died survived for an average period of only six months. No definite conclusions can be drawn from this observation, for it is probable that in many instances the biopsy was performed long after the onset of DGS and does not reflect the true onset of the renal disease.

TABLE IX
FOLLOW-UP DATA

	Diffuse Lesion	Mixed Lesion	Total
No. of patients dead	11 (45.8%)	14 (82.4%)	25
Average age (yr.) at death	52.5	56	54.5
Average duration (yr.) of diabetes (onset to death)	11.7	11.8	11.8
Average duration (yr.) of life with DGS	2.9	6 mo.	1.5
No. of patients alive	7 (29.2%)	2 (11.8%)	9
Average age (yr.) now	42.1	68	55.0
Average duration (yr.) of diabetes (onset to present)	11.0	22	13.4
Average duration (yr.) of life with DGS	2.2	2.0	2.1
No. of patients lost to follow-up	6	1	7

Ten of the twenty-five patients who are dead (five with diffuse and five with mixed DGS) succumbed to some form of renal disease. Eight patients died in uremia secondary to their diabetic nephropathy; two with the mixed form of DGS died of other renal diseases superimposed on their glomerulosclerosis. One of these had a terminal episode of acute tubular necrosis, and in the other acute glomerulonephritis developed.

Nine patients are still alive. All have hypertension and proteinuria, two are nephrotic, and two have azotemia. Four patients have been followed up for two, three, four and eight years, respectively. One of these is uremic; one shows little evidence of renal disease clinically except for proteinuria and slightly elevated blood urea nitrogen; one is not uremic and recently underwent surgery successfully. It is interesting that three of these patients are in their mid-thirties and have had diabetes for fifteen years (one case), and seventeen years (two cases). They all showed a moderately severe diffuse lesion (2 plus) at the time of their last biopsy. The remaining patient is sixty-three years old, has had diabetes for seventeen years, and shows the mixed lesion on renal biopsy.

COMMENTS

Our study indicates that DGS is a more common manifestation of diabetes mellitus than it is generally thought to be. All the diabetic patients in our series underwent biopsy because of some evidence of renal disease, and all but six were found to have DGS. While it is true that the usually accepted clinical criteria were present in many of the cases, fifteen additional patients

who did not show the Kimmelstiel-Wilson syndrome were also found to have diabetic glomerulosclerosis. Only an awareness of the frequency of this entity as a complication of diabetes will allow it to be detected in even greater numbers.

It was our impression at the beginning of this study that pyelonephritis would be found more frequently in diabetic patients than in those with DGS, but this was not borne out in our experience. Using Kleeman's criteria for the diagnosis of pyelonephritis [*34*] we were unable to make this diagnosis in any of the biopsies, and in only three instances was it found at autopsy. Similarly, although we expected to find benign arteriolar nephrosclerosis as the sole lesion in several of our patients, it occurred alone only once. Mild proteinuria and slight azotemia are typical of both of these diseases, but when they occur in a diabetic subject we believe that the most likely diagnosis is DGS.

Diagnosis of DGS. In our series a surprisingly large number of cases were diagnosed accurately prior to biopsy. The patients who proved to have the mixed lesion were diagnosed correctly thirteen times of seventeen. Among five patients with the severe diffuse type of DGS (3 or 4 plus diffuse lesions) only one was misdiagnosed as having membranous glomerulonephritis. Fifty per cent of the patients with less severe diffuse involvement (1 or 2 plus) were diagnosed as DGS prior to biopsy. Thus it is the patients with mild or moderate degrees of DGS on biopsy who present the greatest diagnostic difficulty.

Knowledge of the age at onset of diabetes and the duration of diabetes is not diagnostically helpful, nor has a history of renal disease been of aid to us in making the diagnosis. DGS is not invariably accompanied by hypertension, retinopathy or amelioration of diabetes, and hypoproteinemia is rarely found. In addition, these clinical manifestations are frequently seen in diabetic patients with renal disease other than DGS.

It is interesting that a significant reduction in insulin requirement was found in three of our six diabetic patients with other forms of renal disease as well as in twelve patients with DGS. The cause of apparent improvement in the diabetic state is still not clearly defined. The development of a type of diabetes with different metabolic characteristics has been suggested by Zubrod [*30*]. Others [*32*] believe that it is connected with the decrease in caloric intake, weight loss and altered carbohydrate tolerance which commonly occur with the onset of uremia, the nephrotic syndrome or congestive heart failure. Elgee et al. [*35*] have presented evidence that insulin is most heavily concentrated in the convoluted tubules of the renal cortex and metabolized by the kidney. This suggests that the reduced insulin requirement in DGS may be due to tubular damage (which is frequently seen in DGS, chronic glomerulonephritis and other predominantly glomerular diseases), with resultant failure of insulin degradation and apparently increased insulin sensitivity.

The finding of azotemia is more helpful in differentiating the type of DGS than in making the diagnosis of DGS, as will be discussed subsequently. While DGS of the diffuse type can exist in its milder stages without azotemia, by far the majority of patients in our series had elevated blood urea nitrogen levels.

Proteinuria was the most frequent and the earliest abnormality seen in our patients with DGS. It was the only evidence of renal disease in a few patients, and in others it occurred without azotemia. In addition, in severity it showed a good correlation with the severity of the diffuse lesion. Rogers [*23*] thought that the most reliable clinical criterion of diabetic nephropathy was massive proteinuria. We are of the opinion that the finding of proteinuria of any degree in a diabetic subject should suggest the diagnosis of DGS. If the full nephrotic syndrome or Kimmelstiel-Wilson syndrome is present, the presumptive diagnosis of DGS is further strengthened.

We therefore conclude that the classic clinical criteria for making the diagnosis of DGS are helpful not because they invariably occur, not because they are specific, but because DGS is so frequently found in diabetic subjects with renal disease. Nevertheless, the only definitive way to make the diagnosis of DGS antemortem is by needle biopsy of the kidney.

Differences Between the Diffuse and Mixed Types of DGS. Once the diagnosis of DGS is suspected, certain differences between the two types become apparent. A history of diabetes of more than ten years' duration tends to favor the mixed lesion. In addition, the mixed lesion is more likely to be found in the older (over fifty) age group. Although three patients with the mixed lesion were under fifty years of age, the diagnosis of mixed DGS was made predominantly in the sixth and seventh decades, the majority of patients being between the ages of fifty and sixty-five. In contrast, the peak ages for

the diagnosis of the diffuse lesion were from thirty to thirty-nine years (eight patients) and fifty-five to sixty-five (eight patients). The remainder were scattered through the intervening decades.

All the patients with the mixed lesion were azotemic at the time of biopsy, while only 60 per cent of those with diffuse involvement were found to be so. In addition, the blood urea nitrogen levels were considerably higher in the group with mixed DGS. These observations suggest that although the diffuse lesion may be present when blood urea nitrogen is normal (40 per cent in our series), the mixed lesion is very unlikely in the absence of azotemia. If the blood urea nitrogen value rises above 45 mg. per 100 ml. the chances that the glomerulosclerosis is mixed in type are greater.

Diabetic acidosis was a relatively rare occurrence in the mixed group; only two instances were observed at any time in the course of illness in the latter patients. Only one patient had an episode of diabetic acidosis after the biopsy diagnosis of mixed DGS was made, and his degree of renal insufficiency was not pronounced (blood urea nitrogen 29 mg. per 100 ml.). None of the patients who were acidotic after the diagnosis of diffuse DGS was established had blood urea nitrogen elevations above 30 mg. per 100 ml. It may therefore be true that the greater frequency of acidosis in patients with diffuse DGS is related to their lesser degree of renal insufficiency.

Vascular disease, as manifested by retinopathy, myocardial infarction and peripheral vascular disease, was more prevalent in the group with mixed DGS. Predominantly systolic hypertension was also more common among the latter patients. A significant decrease in insulin requirement was slightly more frequent in the patients with the mixed form of DGS. The incidence of nephrotic syndrome was equally divided among the two groups.

Comparison of Biopsy and Autopsy Results. Fifteen patients, seven with the diffuse and eight with the mixed lesion, had either repeat biopsy or autopsy follow-up. No improvement in the lesion in subsequent specimens was seen, nor was the grading of the repeated biopsy or of the autopsy less than that in the original specimen. Moreover, repeated biopsies did not reveal the development of nodules nor were they found at autopsy in patients who had only the diffuse lesion at the time of the first biopsy. In one patient with diffuse DGS, whose total follow-up period has been eight years and who has had four biopsies over a five-year span, nodules have failed to develop.

Specificity of the Lesions. In over 500 biopsies in patients with almost every type of renal disease we have seen no patient with either diffuse or mixed DGS who has not had diabetes. Some observers have reported the presence of nodules such as are seen in mixed DGS in other diseases of the kidney [*8,37*]. LaCompte [*20*] points out that when nodular glomerulosclerosis is described in non-diabetic subjects it is usually the exudative lesion that is seen, for it closely resembles the nodular lesion but is not specific for diabetes. (Fig. 1H.) Patients in whom "improvement" has occurred in their diabetes with the onset of DGS may require diligent searching to prove the presence of the diabetic state [*36,38*].

Need for Follow-up. The fact that DGS seems, in some instances, to develop at a fairly slow rate points up the necessity for long-term biopsy follow-up of these patients. Only in this manner can the pathogenesis of the lesions be determined, and the still obscure relationship of the diffuse to the mixed lesion be clarified. There are many clinical similarities which suggest that the mixed lesion may be simply a more advanced stage of the diffuse process. Only by means of repeated biopsies over a period of several years will this question be answered.

Prognosis. The age at onset of diabetes, the duration of diabetes from onset to death, and the age at death are very similar when the two types of DGS are compared. The average age at death of the patients with DGS as a whole was in the first half of the fifth decade. This represents a considerably poorer survival than in the general diabetic population, which now has a life expectancy only slightly less than normal [*21*]. Once DGS has developed, the patients with the mixed type are usually sicker, have more vascular disease, more azotemia, more proteinuria and more congestive heart failure. The adequacy of control of the diabetes did not appear to influence the severity of the pathologic lesion. Although adequacy of control was difficult to assess, particularly in retrospect, those patients whose insulin requirements remained constant and whose blood sugar levels were normal showed as severe a degree of DGS as those requiring large doses of insulin and consistently exhibiting hyperglycemia.

SUMMARY

Sixty-four needle biopsies of the kidney were performed in fifty-seven diabetic patients with evidence of renal disease. Forty-one patients were found to have diabetic glomerulosclerosis (DGS); six patients had other forms of renal disease.

Two forms of DGS were characterized: a diffuse and a mixed (diffuse and nodular) type. There was no evidence to suggest that the mixed lesion developed from the diffuse lesion. The location of the hyaline deposits in the glomeruli remains unsettled by this study.

Clinically, proteinuria was the earliest and most persistent abnormality. A history of diabetes of more than ten years' duration, the rare occurrence of acidosis, and the presence of blood urea nitrogen values above 45 mg. per 100 ml. tended to suggest the mixed rather than the diffuse lesion.

The only conclusive method of making the diagnosis of DGS antemortem is by needle biopsy of the kidney. The accuracy of renal biopsy for diagnosis and follow-up was supported by the similar findings in those patients in whom autopsy was performed. The need for long-term follow-up of patients with DGS with repeated renal biopsies is stressed.

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Comparative Study of Serum Leucine Aminopeptidase, 5-Nucleotidase and Non-specific Alkaline Phosphatase in Diseases Affecting the Pancreas, Hepatobiliary Tree and Bone*

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Serum leucine aminopeptidase (LAP) has been reported to be strikingly elevated in patients with carcinoma of the pancreas [*1*], as well as in patients with a wide variety of diseases of the hepatobiliary tract [*2–6*]. Histochemically, the concentration of leucine aminopeptidase (LAP), 5-nucleotidase (5N) and non-specific alkaline phosphatase (AP) is intense in the bile ducts and bile canaliculi, and weak in the parenchymal cells [*7,8*]. These findings suggested comparable changes in serum activities of these three enzymes in diseases of the liver, biliary tract and pancreas, dependent upon whether the pathology involved primarily the ductal system or the parenchyma of the liver.

The purposes of this study were to measure the activity of LAP in the serum of normal subjects, and in patients in whom AP is elevated, either due to a variety of inflammatory, malignant or granulomatous diseases affecting the liver, biliary tract and/or the pancreas, or to disease affecting bone such as metastatic carcinoma, Paget's disease or osteomalacia secondary to non-tropical sprue; and further, to compare these results with the simultaneous measurement of 5N, since the serum level of this enzyme is normal in diseases affecting bone [*9,10*].

MATERIALS AND METHODS

All serum was obtained from normal healthy subjects in the fasting state, and from patients on the medical and surgical pavilions of the New York Hospital-Cornell Medical Center also in the fasting state. The diagnoses in the latter were confirmed either by biopsy, surgical exploration, autopsy, metastatic bone series, or their respective clinical courses. In all, sixty-five normal subjects (forty men and twenty-five women) and 353 patients with a variety of diseases affecting the bone, the liver, the biliary tract and the pancreas were studied.

The categories of diseases and the number of patients studied were as follows:

Group A. Diseases of the pancreas: Carcinoma of the head of the pancreas with obstruction of the common bile duct, ten; metastases to the liver, five; carcinoma of the body and tail of the pancreas with metastases to the liver, five; carcinoma of the head, body and/or tail of the pancreas without obstruction and without metastases to the liver, six; acute pancreatitis, six; and chronic relapsing pancreatitis, four.

Group B. Diseases of the liver: Acute viral hepatitis, twenty-four; hepatitis with intrahepatic cholestasis, eight; anicteric hepatitis, two; toxic drug hepatitis, six (iproniazid, one; chlorpromazine, three; triethylene thiophosphoramide, one; and Actinomycin D,® one); Laennec's cirrhosis, thirty-six; Laennec's cirrhosis with acute fatty infiltration, twenty; and primary biliary cirrhosis, eighteen.

Group C. Disease of the biliary tract: Choledocholithiasis, ten; calculous cholecystitis with jaundice, eight; stricture of the common bile duct, two; carcinoma of the biliary tree, four; carcinoma of the gallbladder, two; and stenosing cholangitis, two.

Group D. Carcinoma, non-metastatic to the liver or bone: Lung, eighteen; stomach, ten; uterus, six; breast, ten; colon, nine; kidney, four; and urinary bladder, four.

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Group E. Carcinoma of liver, primary or metastatic: Primary hepatoma, two; metastatic disease from colon, twelve; stomach, six; lung, eight; and breast, eight.

Group F. Metastatic carcinoma to bone: Uterus, three; prostate, four; lung, six; and breast, eight.

Group G. Infiltrative disease of the liver: Lymphosarcoma, ten; tuberculosis, two; Hodgkin's disease, six; systemic lupus erythematous, two; and sarcoidosis, five.

Group H. Miscellaneous group of patients with diseases with elevated non-specific alkaline phosphatase: Non-tropical sprue with osteomalacia, eight; Paget's disease, twenty; osteogenesis imperfecta, two; and acromegaly, two.

AP and 5N levels were determined by the method of Dixon and Purdom [*9*], with the following modifications: 0.3 ml. of 0.05M $MgSO_4$ was substituted for 0.3 ml. of H_2O in both the pH 9.3 and 7.5 beta-glycerophosphate substrate systems, while 0.3 ml. of 0.4M $MgSO_4$ was used for the pH 7.5 adenosine-5-phosphate substrate system. Preliminary observations demonstrated that 0.3 ml. of 0.4M $MgSO_4$ was required to obtain optimum activity of 5N in serum from both normal and diseased subjects. At this concentration of $MgSO_4$, there was 100 per cent inhibition of AP at both pH 9.3 and 7.5. Thus the rate of hydrolysis of adenosine-5-phosphate was determined at pH 7.5 in the presence of 0.4M magnesium ion and the unit of 5N activity was defined as 1 mg. of phosphate ion, liberated in two and a half hours, analogous to the Bodansky unit for AP activity. Accordingly, 5N and AP activities in the serum are both expressed in Bodansky units.

LAP activity was determined by the method of Goldbarg and Rutenberg [*11*] at pH 7.1, utilizing a chromogenic substrate, 1-leucyl-beta-naphthylamide hydrochloride. The beta-naphthylamine liberated by enzymatic hydrolysis was assayed by a modified Bratton-Marshall reaction. LAP activity is expressed in units.

A Coleman Junior Spectrophotometer Model 6A, with microcuvettes was used in all determinations.

RESULTS

Table 1 summarize the activities in the serum of AP, 5N and LAP in normal adults and in patients with diseases affecting the bone, pancreas and the hepatobiliary tree. The range and mean of normal values for LAP, 5N and AP were 76 to 180 (127.7 ± 30.8) units, 0.4 to 2 (1 ± 0.3) Bodansky units, and 1.2 to 4.2 (3 ± 0.7) Bodansky units, respectively. These findings are in general agreement with those previously reported [*1,9*].

Group A. Diseases of the pancreas: Significant changes in levels of these enzymes in patients with *carcinoma of the pancreas* depended to a large extent upon whether or not the disease had obstructed the common bile duct and/or metastasized to the liver. Thus in the ten patients with *carcinoma of the head of the pancreas* with *obstruction* of the common bile duct, the values for LAP, 5N and AP were 270 to 804 (441 ± 166) units, 5.9 to 34.6 (14 ± 9) and 6.6 to 20.8 (14 ± 5.3) Bodansky units, respectively. Similar results were obtained in five patients with carcinoma of the head and five with carcinoma of the body and tail, all of whom had *metastases* to the liver, but were *anicteric*, the values for LAP, 5N and AP being 248 to 840 (416 ± 247) units, 3.9 to 22 (11.4 ± 7.1) and 6 to 18.2 (10.9 ± 5.2) Bodansky units, respectively in the former group, and 290 to 420 (368 ± 69) units, 7.8 to 12 (9.3 ± 3.3) and 6.5 to 13 (8.9 ± 3.5) Bodansky units in the latter group. (Table 1, Fig. 1.)

Of great significance was the fact that in six patients with *carcinoma of the head and/or body of the pancreas* with neither metastases to the liver nor obstruction of the common bile duct, 5N was normal in four, and LAP and AP were normal in all; the elevations of 5N in two patients were slight, namely, 2.5 and 2.6 Bodansky units.

Pancreatitis: The six patients with *acute pancreatitis* had values for LAP, 5N and AP of 155 to 420 (265 ± 106) units, 3 to 12.5 (5.6 ± 3.6) and 4 to 13.5 (6.6 ± 3.5) Bodansky units, respectively. Of note is the fact, that in the four patients with some degree of obstruction of the common bile duct (serum total bilirubin levels were 2 to 6.5 mg. per cent,) the values for these enzymes were uniformly high. (Fig. 1.) In two anicteric patients with normal LAP and AP levels, 5N was elevated. Four anicteric patients with *chronic relapsing pancreatitis* had normal values for all three enzymes.

Group B. Diseases of the liver (Table 1, Fig. 2): The levels of serum LAP, 5N and AP in twenty-four patients with *acute viral hepatitis*, all of whom were in the active stage of their disease as judged by liver biopsy and significant elevations of serum glutamic oxaloacetic transaminase (SGOT), varied widely. LAP ranged from 152 to 595 (318 ± 92) units. Six patients had levels below 250 units, and in two patients the LAP was normal. (Fig. 2.) It is possible that in these latter cases the peak of LAP activity might have been missed. The values for 5N and AP were 1.5 to 19.3 (6.2 ± 4.1) and 3 to 8.5 (5.7 ± 1.6) Bodansky units, respectively. In the two patients with normal LAP, 5N and AP were normal as well.

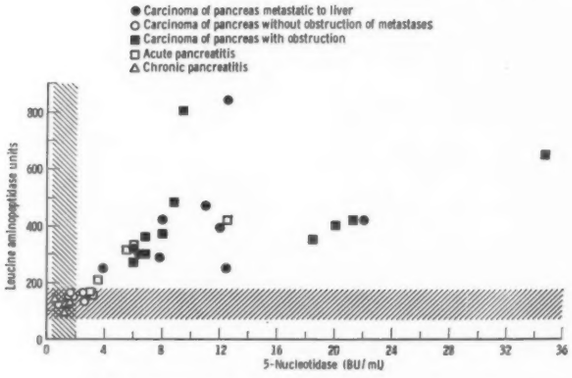


FIG. 1. LAP versus 5N in diseases of the pancreas. Significant elevations are noted in carcinoma with obstruction or metastases. High levels in pancreatitis were associated with jaundice. Cross-hatched areas represent the normal range.

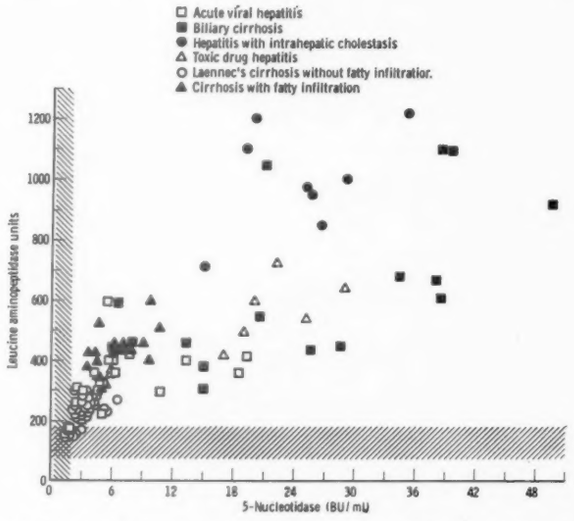


FIG. 2. LAP versus 5N in diseases of the hepatobiliary tree. In viral hepatitis, in contrast to conditions with intrahepatic cholestasis, the level of these enzymes did not correlate with degree of bilirubin retention. Cross-hatched areas represent the normal range.

However, in the eight patients with *intrahepatic cholestasis* presumably secondary to viral hepatitis, there was consistent and marked elevation of the serum levels of all three enzymes, LAP being 710 to 1220 (1,000 ± 93) units; 5N, 15 to 35 (28 ± 4) Bodansky units, and AP, 12 to 33 (25.5 ± 4.2) Bodansky units. (Fig. 2.) Similar elevations of LAP, 5N and AP were found in six patients with "*toxic*" *drug hepatitis*, the values being 430 to 728 (578 ± 90) units, 17 to 29 (22 ± 4.3) and 20 to 30 (25 ± 3.7) Bodansky units, respectively. (Fig. 2.)

Twenty patients with *Laennec's cirrhosis* and *acute fatty infiltration of the liver*, all of whom were jaundiced, had LAP levels greater than 300 units, the values being 310 to 600 (415 ± 79) units. Significant concomitant elevations were also recorded for 5N and AP, 3.5 to 10.6 (5.8 ± 1.9) and 5 to 12.5 (6.6 ± 2.7) Bodansky units, respectively. (Table 1, Fig. 2.) In contrast, the corresponding mean serum levels of all three enzymes in patients with Laennec's cirrhosis with varying degrees of fibrosis but *without* acute fatty infiltration, although elevated, 237 ± 43 units, 3.3 ± 1.3 and 5.4 ± 0.8 Bodansky units were consistently lower than those of the former group of patients. Further, in the latter group LAP was normal in eight, 5N in five and AP in four. (Fig. 2.)

Eighteen patients with *primary biliary cirrhosis* at various stages of the disease were studied. The values for LAP, 5N and AP were 310 to 1098 (642 ± 275) units, 6.1 to 49.3 (23.8 ± 14.8) and .7 to 28.1 (16.5 ± 7.46) Bodansky units, respectively. (Table 1, Fig. 2.)

Group C. Biliary tract disease: This group of twenty-eight patients, all with varying degrees of jaundice, showed striking elevations of LAP, 5N and AP. Ten patients with choledocholithiasis had values of LAP, 5N and AP of 206 to 950 (431 ± 296) units, 2.7 to 28.5 (9 ± 7) and 5.6 to 30.5 (12.7 ± 10) Bodansky units, respectively. (Table 1.) Thus the mean value for LAP in this group was the same as for carcinoma of the pancreas with obstruction of the common bile duct.

Group D. Carcinoma, without metastases to liver or bone: Sixty-one patients with carcinoma of lung, stomach, breast, uterus, colon, kidney or urinary bladder were studied in this group. The values for LAP, 5N and AP were normal in all, being 88 to 160 (121 ± 15) units, 0.5 to 1.5 (1 ± 0.2) and 2.2 to 4.2 (3.6 ± 0.2) Bodansky units, respectively. (Table 1.)

Group E. Carcinoma, metastatic to the liver: Thirty-six patients with metastatic carcinoma of the liver were studied. Significant elevations of LAP were obtained in thirty-two, the spread being 132 to 942 (441 ± 150) units; LAP was normal in two patients. The 5N and AP values were abnormal in all thirty-four, being 3.3 to 36.1 (12.5 ± 6.1) and 5.7 to 35 (13.6 ± 7.1) Bodansky units, respectively. (Table 1.) Twenty-eight of these patients with liver metastases were anicteric, while all thirty-four had abnormal retention of bromsulfalein.

Group F. Carcinoma, metastatic to bone: Twenty-one patients with metastatic bone disease were studied. LAP and 5N were normal in all, with

TABLE I

SERUM LEUCINE AMINOPEPTIDASE (LAP), 5-NUCLEOTIDASE (5N) AND NON-SPECIFIC ALKALINE PHOSPHATASE (AP) LEVELS

Diagnosis	No. Patients Studied	LAP (units)		5N (Bodansky units/100 ml.)		AP (Bodansky units/100 ml.)	
		Range	Mean ± S.D.	Range	Mean ± S.D.	Range	Mean ± S.D.
Normal Subjects							
	65	76–180	127.7 ± 30.8	0.4 – 2.0	1.0 ± 0.3	1.2– 4.2	3.0 ± 7
Group A. Patients with Diseases of the Pancreas							
Carcinoma of the head of the pancreas with obstruction of the extrahepatic biliary tract	10	270–804	441 ± 166	5.9 –34.6	14.0 ± 9.0	6.6–20.8	14.0 ± 5.3
Metastatic to the liver	5	248–840	416 ± 247	3.9 –22.0	11.4 ± 7.0	6.0–18.2	10.9 ± 5.2
Without obstruction or metastasis	6	120–160	146 ± 16	0.75– 2.6	1.8 ± 0.6	2.2– 4.4	3.5 ± 0.8
Carcinoma of the body and tail with metastasis to the liver	5	290–420	368 ± 69	7.8 –12.0	9.3 ± 3.3	6.5–13.0	8.9 ± 3.5
Acute pancreatitis	6	155–420	265 ± 106	3.0 –12.5	5.6 ± 3.6	4.0 13.5	6.6 ± 3.5
Chronic pancreatitis	4	91–135	118 ± 19	0.6 – 1.6	1.2 ± 0.4	2.0– 4.2	3.4 ± 1.0
Group B. Patients with Diseases of the Liver							
Acute viral hepatitis	24	152–595	318 ± 92	1.5 –19.3	6.2 ± 4.1	3.0– 8.5	5.7 ± 1.6
Laennec's cirrhosis	36	144–302	237 ± 43	1.3 – 6.5	3.3 ± 1.3	2.1– 9.1	5.4 ± 1.8
Laennec's cirrhosis with acute fatty infiltration	20	310–600	415 ± 79	3.5 –10.6	5.8 ± 1.9	5.0–12.5	6.6 ± 2.7
Hepatitis with intrahepatic cholestasis	8	710–1220	1000 ± 93	15.0 –35.0	28.0 ± 4.0	12.0–33.0	25.4 ± 4.2
Primary biliary cirrhosis	18	310–1098	642 ± 275	6.1 –49.3	23.8 ± 14.8	6.7–28.1	16.5 ± 7.4
"Toxic" drug hepatitis	6	430–728	578 ± 90	17.0 –29.0	22.0 ± 4.3	20.0–30.0	25.0 ± 3.7
Anicteric hepatitis	2	366; 340		2.7; 3.9		6.5; 5.9	
Group C. Patients with Diseases of the Biliary Tract							
Choledocholithiasis with jaundice	10	206–950	431 ± 296	2.7 –28.5	9.0 ± 7.0	5.6–30.5	12.7 ± 10.0
Calculous cholecystitis with jaundice	8	207–477	302 ± 144	2.6 – 8.7	5.1 ± 3.2	6.0–11.0	8.0 ± 2.8
Common duct stricture	2	423; 447		28.5; 16.6		15.6; 8.8	
Carcinoma of the biliary tree	4	352–628	511 ± 134	27.4 –43.0	34.0 ± 7.8	16.2–51.5	27.6 ± 18.6
Carcinoma of the gallbladder	2	395; 450		13.5; 14.5		9.0; 15.0	
Stenosing cholangitis	2	590; 470		13.2; 9.0		14.2; 14.0	
Group D. Patients with Carcinoma, Non-metastatic to Liver or Bone							
Neoplasia, non-metastatic	61	88–160	121 ± 15	0.5 – 1.5	1.0 ± 0.2	2.2– 4.2	3.6 ± 0.2

TABLE 1 (*Continued*)

SERUM LEUCINE AMINOPEPTIDASE (LAP), 5-NUCLEOTIDASE (5N) AND NON-SPECIFIC ALKALINE PHOSPHATASE (AP) LEVELS

Diagnosis	No. Patients Studied	LAP (units)		5N (Bodansky units/100 ml.)		AP (Bodansky units/100 ml.)	
		Range	Mean ± S.D.	Range	Mean ± S.D.	Range	Mean ± S.D.
Group E. Patients with Carcinoma of Liver, Primary or Metastatic							
Neoplasia metastatic to liver	36	132–942	441 ± 150	3.3 –36.1	12.5 ± 6.1	5.7–35.0	13.6 ± 7.1
Group F. Patients with Metastatic Carcinoma to Bone							
Neoplasia with skeletal metastases	21	80–169	125 ± 19	0.2 – 1.6	0.9 ± 0.24	7.2–36.1	15.5 ± 5.8
Group G. Patients with Infiltrative Disease of Liver							
Lymphosarcoma	10	158–367	258 ± 82	3.0 –11.0	5.1 ± 2.9	4.5–13.9	9.6 ± 4.0
Sarcoidosis	5	132–328	243 ± 171	2.7 –17.0	8.3 ± 6.0	2.7–14.8	8.3 ± 5.9
Tuberculosis	2	367; 364		4.6; 21.9		7.5; 18.2	
Hodgkin's disease	6	276–628	410 ± 123	3.6 –23.5	12.3 ± 6.7	5.6–30.6	14.8 ± 8.6
Systemic lupus erythematosus	2	217; 238		2.4; 4.8		4.7; 3.3	
Group H. Patients with Diseases with Elevated AP Levels							
Paget's disease	20	90–160	119 ± 20	0.2 – 1.2	0.6 ± 0.32	5.1–85.0	24.9 ± 20.0
Acromegaly	2	96; 110		0.8; 0.4		5.8; 10.0	
Osteogenesis imperfecta	2	72; 120		0.6; 0.9		5.9; 6.2	
Non-tropical sprue	8	75–152	114 ± 26	0.3 – 1.6	0.9 ± .04	4.7–10.8	8.2 ± 2.4

values of 80 to 169 (125 ± 19) units, and 0.2 to 1.6 (0.9 ± 0.24) Bodansky units, respectively. In contrast, AP was uniformly elevated, 7.2 to 36.1 (15.5 ± 5.8) Bodansky units. (Table 1.) Of great interest are the results in eight patients with metastatic disease to both bone and liver, the values for LAP, 5N and AP being 132 to 490 (371 ± 159) units, 4.2 to 7.5 (5.5 ± 1.3) and 6.2 to 20.4 (13.7 ± 6.8) Bodansky units, respectively. In this group two patients had normal levels of LAP, but the 5N and AP levels were abnormal in all.

Group G. Infiltrative diseases of the liver: In ten patients with *lymphosarcoma* involving the liver, the values for LAP, 5N and AP were 158 to 367 (258 ± 82) units, 3 to 11 (5.1 ± 2.9) and 4.5 to 13.9 (9.6 ± 4) Bodansky units, respectively. (Table 1.) Two of these patients had normal levels of LAP. Similar elevations were found in five patients with *sarcoidosis*, two with *tuberculosis*, six with *Hodgkin's disease* and two with *systemic lupus erythematosus*. One of the patients with sarcoidosis had normal LAP and AP levels.

Group H. Miscellaneous: This group was comprised of thirty-two patients including twenty patients with *Paget's disease*, two with *acromegaly*, two with *osteogenesis imperfecta* and eight with *osteomalacia secondary to non-tropical sprue*. All of these patients had normal levels of LAP and 5N, whereas the AP was elevated in all. (Table 1, Fig. 3.)

COMMENTS

Serum LAP has been reported to be elevated in patients with carcinoma of the pancreas [*1,2*].

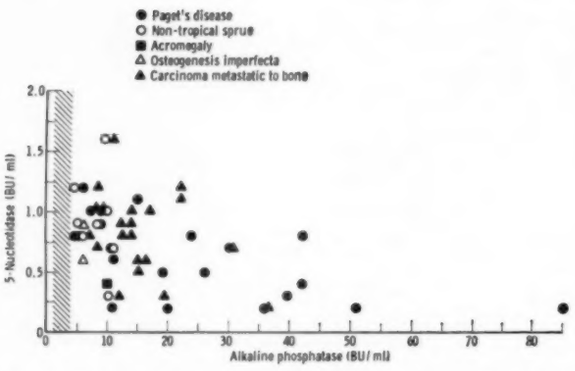


FIG. 3. 5N versus AP in diseases affecting bone. Note that 5N is normal in all instances. Cross-hatched area represents the normal range.

Our results, as well as those of Pineda [*2*], Shay [*3*], Fleisher [*4*], Arst [*5*] and Harkness et al. [*6*], demonstrate, however, that elevation of LAP is not confined to carcinoma of the pancreas; indeed, it is high in a number of diseases of the pancreas and the hepatobiliary tract, in which 5N and AP levels are also abnormal. Such conditions are characterized by the following anatomical abnormalities: (1) extrahepatic biliary tract obstruction, (2) intrahepatic cholestasis, (3) infiltrative and metastatic disease of the liver, and (4) liver cell necrosis.

Extrahepatic Obstruction. Of the twenty-six patients with carcinoma of the pancreas studied, twenty had elevated levels of LAP, 5N and AP. Ten had varying degrees of hyperbilirubinemia; all ten who were not jaundiced, had metastases to the liver. The six patients with normal LAP and AP levels had neither common duct obstruction nor metastases to the liver at the time of the determinations. Thus serum LAP is elevated in carcinoma of the pancreas only when there is some degree of obstruction of the common bile duct or metastases to the liver, a finding which agrees with the recent published studies of Shay et al. [*3*]. We take exception with the statement of Pineda et al. [*2*] that a serum LAP less than 450 units tends to exclude carcinoma of the head of the pancreas in the differential diagnosis of jaundice. Using this criterion we would have missed the diagnosis in six of ten patients. That obstruction of the common bile duct does indeed play a major role in elevating these enzymes is borne out by the elevated levels of LAP, 5N and AP in the ten patients with choledocholithiasis and jaundice. In all ten of these patients these enzymes returned to normal levels within three weeks of removal of the stones.

Intrahepatic Cholestasis. Fleisher et al. [*4*] found striking elevations of LAP in acute viral hepatitis. Our measurements of LAP, however, varied widely in twenty-four patients with disease, being normal in two patients. It is conceivable that the elevations of LAP with concomitant elevations in 5N and AP may well reflect the degree of cholestasis present in these patients and may well account for the wide range of levels that were found. LAP was markedly elevated in eight patients with cholangiolitic hepatitis, eighteen with biliary cirrhosis and six with "toxic" drug hepatitis. The findings in these diseases may be explained readily by intrahepatic cholestasis, a contention which is supported by parallel changes in serum 5N and AP. Of significance in this regard is that only those patients with Laennec's cirrhosis with fatty infiltration had elevations of all three enzymes, results which are consistent with the observations of Philips et al. [*12*] and Popper et al. [*13*] that many of the manifestations of acute fatty infiltration in chronic alcoholics are due to intrahepatic cholestasis. Again, intrahepatic cholestasis is the basis for elevations of LAP, as well as 5N and AP.

Infiltration of Liver. Infiltrative diseases of the liver are characterized by elevated levels of alkaline phosphatase and bromsulfalein retention [*14*]. In our group of patients with tuberculosis, lymphosarcoma, Hodgkin's disease, sarcoidosis and systemic lupus erythematosus, there was elevation of 5N and AP in all cases; LAP was normal in two patients with lymphosarcoma, two with sarcoidosis and one with systemic lupus erythematosus.

Metastases to Liver. Elevated levels of serum LAP, 5N and AP were found in patients with carcinoma of the pancreas, colon, breast and lung metastatic to the liver. Rutenburg et al. [*1*], as well as Shay et al. [*3*], attribute the elevation of serum LAP in such patients to intrahepatic biliary radicle obstruction. We believe that the finding of concurrent elevations of 5N and AP lends some support to this hypothesis.

Liver Cell Necrosis. Two patients with anicteric hepatitis had elevated levels of LAP, 5N and AP, besides the group of twenty-four patients with acute infectious hepatitis with varying degrees of jaundice. It is conceivable that liver cell necrosis may contribute to elevated levels of LAP, 5N and AP. However, it is our impression that the major source of the elevated serum levels of these enzymes comes from some degree

of associated intrahepatic cholestasis in these conditions.

The further usefulness of simultaneous determinations of 5N, LAP and AP is clearly demonstrated in the group of patients with elevated serum alkaline phosphatase due to disease of the skeletal system. This group of patients with Paget's disease, osteogenesis imperfecta, metastatic disease to bone and osteomalacia secondary to non-tropical sprue consistently had elevations of serum AP, but normal levels of 5N and LAP. Thus the source, bone or liver, of an elevated alkaline phosphatase can be ascertained. These findings confirm the previous publications of Dixon and Purdom [*9*] and of Young [*10*]. It should be pointed out, however, that when disease affects both bone and liver, as in our eight patients with metastatic disease to both bone and liver, the level of all three enzymes may be elevated.

SUMMARY

Serum leucine aminopeptidase activity (LAP) is increased in a variety of diseases of the pancreas and hepatobiliary tract characterized by either intrahepatic or extrahepatic obstruction of the biliary tree or by infiltration or metastasis to the liver. Serum LAP is normal in carcinoma of the pancreas, if neither obstruction of the common bile duct nor metastasis to the liver has taken place.

Elevation of serum LAP is closely paralleled by rises in serum 5-nucleotidase (5N) and non-specific alkaline phosphatase (AP). This finding further indicates the effect of biliary stasis upon LAP levels. LAP and 5N were highest in conditions characterized by intrahepatic cholestasis: biliary cirrhosis, "cholangiolitic" hepatitis, "toxic" drug hepatitis and Laennec's cirrhosis with fatty infiltration.

Simultaneous determination of non-specific AP with LAP and 5N is of value in determining the cause for elevation of the former, i.e., whether due to liver or bone disease.

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Manifestations of Metastatic Tumors of the Liver*

A Study of Eighty-One Patients Subjected to Needle Biopsy

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Considering the frequency with which metastatic tumors of the liver are known to occur, and the difficult diagnostic problems they often pose, surprisingly little has been written about their clinical features. Although early recognition of such metastases does not alter the usually hopeless prognosis, it does avert futile attempts to extirpate the primary tumor, and obviates the need for extensive diagnostic procedures. In this connection needle biopsy of the liver has proved to be of great value.

To delineate the clinical and laboratory features of intrahepatic metastatic tumors and to evaluate further the diagnostic accuracy and safety of needle biopsy of the liver in such cases, the records of eighty-one patients with proved metastatic tumor of the liver who were subjected to needle biopsy have been reviewed.

MATERIAL

Eighty-one patients with proved intrahepatic metastatic carcinoma or sarcoma were seen by members of the Liver Study Unit of the Grace-New Haven Community Hospital during the period 1948 to 1960. These were selected for analysis since a needle biopsy specimen and detailed clinical and laboratory data bearing on the status of the liver were available in each instance. Patients with intrahepatic Hodgkin's disease or other lymphomas were omitted from consideration. The presence of intrahepatic metastatic tumor was confirmed histologically at the time of biopsy in sixty-three patients, and within a period of six months by direct visualization of the tumor in the course of an exploratory laparotomy, or at necropsy in the remainder.

As might be expected, approximately 95 per cent of the patients were over forty, and 58 per cent were over sixty years of age. There was a slight preponderance of men over women that was not considered significant.

The site of the primary tumor was established with reasonable certainty in 80 per cent of the patients. (Table I.) The failure to establish the site of origin in the others was due largely to the fact that further diagnostic procedures often were abandoned once the presence of hepatic metastases was demonstrated by needle biopsy.

Routine tests of liver function were carried out as described previously [*1*]. For the purposes of this study values in excess of the following were considered abnormal: total serum bilirubin, 1.3 mg. per cent; bromsulphalein (BSP) retention at forty-five minutes after an intravenous injection of 5 mg./kg., 5 per cent; cephalin-cholesterol flocculation, 1 plus at twenty-four hours and 2 plus at forty-eight hours; thymol turbidity, 4 units; serum alkaline phosphatase, 8.9 Shinowara-Jones-Rinehart units, or 4.9 Bodansky units; serum glutamic oxalacetic transaminase, 40 Karmen units; serum globulin, 4 gm. per cent. The lower limit of normal for serum albumin was taken as 3 gm. per cent.

In all patients liver biopsy was performed with a Vim-Silverman needle, usually through an intercostal space in the right posterior or mid-axillary line. The specimen was fixed in Carnoy's solution, embedded in paraffin, sectioned at 5 μ. and stained routinely with both hematoxylin and eosin and Masson's trichrome stain. In many instances serial sections were cut, our practice being to cut as many as eighty to one hundred sections if carcinoma or other focal lesions are suspected.

Significant fever was defined as an elevation of body temperature to 100.6°F. per rectum, or above, on at least three consecutive days. Such fever was attributed to the presence of tumor when infection was excluded

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TABLE I
SITE OF ORIGIN OF HEPATIC METASTASES IN EIGHTY-ONE PATIENTS SUBJECTED TO NEEDLE BIOPSY OF THE LIVER

	No.	Positive Biopsy*
Primary tumors drained by portal vein	37	21 (57%)
Pancreas	16	7 (44%)
Colon and rectum	11	7 (64%)
Stomach	6	5 (83%)
Gallbladder and bile ducts	4	2 (50%)
Primary tumors drained by systemic veins	27	24 (89%)
Lung	12	11 (92%)
Breast	10	9 (90%)
Melanoma of eye	2	2 (100%)
Carotid body	1	0 ...
Uterus	1	1 (100%)
Retroperitoneal fibrosarcoma	1	1 (100%)
Site of primary tumor not determined	17	15 (88%)

* Initial biopsy specimen only.

TABLE II
MAJOR SYMPTOMS IN EIGHTY-ONE PATIENTS WITH PROVED INTRAHEPATIC METASTATIC TUMORS

Symptoms referable to the liver		54 (67%)
Hepatic pain	29 (36%)	
With jaundice	6	
With ascites	5	
With a mass	4	
Ascites	25 (31%)	
With edema	11	
With hepatic pain	6	
With a mass	3	
With jaundice	2	
Jaundice	22 (27%)	
With hepatic pain	8	
With pruritus	6	
With ascites	3	
Palpable or visible abdominal mass	6 (7%)	
With hepatic pain	3	
With ascites	1	
Localizing symptoms referable to primary tumor or extrahepatic metastases		26 (32%)
Non-specific complaints suggestive of neoplastic disease		77 (95%)
Weight loss	65 (80%)	
Anorexia	56 (69%)	
Gastrointestinal symptoms	50 (62%)	
Fever	19 (23%)	

by clinical observation, cultures of the urine and blood, and a roentgenogram of the chest.

The physical findings tabulated were those recorded by members of the Liver Study Unit, who used a standard form for recording detailed clinical, laboratory and histologic data in all cases. The liver was considered abnormal if (1) its lower edge descended more than 2 fingerbreadths below the costal margin in the right mid-clavicular line on deep inspiration, (2) it was indurated or tender, or (3) it contained palpable nodules.

SYMPTOMS

The major symptoms encountered in the group are summarized in Table II. It is noteworthy that fifty-four of the eighty-one patients (67 per cent) had complaints attributable to tumor in the liver, although in many instances these were overshadowed by symptoms referable to the primary tumor or to extrahepatic metastases.

Presenting Complaints. As indicated in Table III, 44 per cent of the group sought medical attention because of symptoms referable to the liver. The latter included pain in the right upper quadrant of the abdomen in 27 per cent, ascites in 9 per cent, jaundice in 6 per cent, and the presence of a palpable or visible mass in the abdomen, which proved to be an enlarged liver, in 2 per cent.

Although a high proportion of the remaining 56 per cent of the patients subsequently were found to have clinical and/or laboratory evidence of hepatic involvement by tumor, 32 per cent consulted a physician because of localizing symptoms referable to the primary tumor or to extrahepatic metastases, and 23 per cent because of non-specific symptoms of the type often associated with neoplasms. Of particular interest in the latter group was fever, which was the major complaint in 7 per cent of the group.

Abdominal Pain. Of the symptoms referable to the liver, pain was the most common, having occurred in twenty-nine of the eighty-one patients (36 per cent), and also was the one that most often led the patient to consult a physician. In almost half this group the pain was accompanied by other symptoms indicative of hepatic disease, including jaundice in six, ascites in five and a palpable or visible mass in the region of the liver in four.

In most patients the pain was localized in the right upper quadrant of the abdomen, was intermittent and sharp in character, often radiated through to the right infrascapular area or around into the right flank, and usually was aggravated by deep breathing, coughing or changes in posture. Often it was accompanied

TABLE III

PRINCIPAL COMPLAINT FOR WHICH EIGHTY-ONE PATIENTS WITH PROVED INTRAHEPATIC METASTATIC TUMORS SOUGHT MEDICAL ADVICE

Symptoms referable to the liver		36 (44%)
Abdominal pain or tenderness in right upper quadrant	22 (27%)	
Ascites	7 (9%)	
Jaundice	5 (6%)	
Abdominal mass (liver)	2 (2%)	
Localizing symptoms referable to the primary tumor or extrahepatic metastases		26 (32%)
Non-specific symptoms suggestive of neoplastic disease		19 (23%)
Fever	6 (7%)	

TABLE IV

SITE OF PRIMARY TUMOR IN NINETEEN PATIENTS WITH HEPATIC METASTASES ASSOCIATED WITH FEVER

Site	No.
Pancreas	4
Melanoma of eye	2
Colon	2
Breast	1
Stomach	1
Gallbladder	1
Carotid body	1
Retroperitoneal fibrosarcoma	1
Unknown	6

by local tenderness in the same area. A few patients complained of a constant dull aching pain, or of a "dragging" sensation beneath the right costal margin.

Ascites. Although ascites was evident in almost a third of the group (27 per cent), only seven of the patients were aware of its presence and regarded it as one of their major complaints. Of the twenty-five patients with demonstrable ascites, nine had other symptoms referable to the liver, including abdominal pain in the right upper quadrant in five, jaundice in two and a subcostal mass in two.

Jaundice. Twenty-two patients (27 per cent) had overt jaundice, but only fourteen were aware of its presence, and only five considered it their major complaint. The jaundice was accompanied by pain in the region of the liver in nine, pruritus in six and ascites in three.

Abdominal Mass. Six patients noted the presence of an abdominal mass which proved to be an enlarged liver. In three the mass was associated with pain and in one with ascites. Two of the patients consulted a physician because of the mass.

Localizing Symptoms Referable to the Primary Tumor or to Extrahepatic Metastases. Twenty-six of the patients (32 per cent) consulted a physician because of symptoms related to the primary tumor or to metastases in extrahepatic sites. However, one-third of these had additional symptoms referable to the liver, including ascites in five, jaundice in four and hepatic pain in one.

Non-specific Symptoms. As indicated in Table II, seventy-seven of the patients (95 per cent) complained of anorexia, weight loss and/or gastrointestinal symptoms. In some, these were clearly due to the primary tumor or to extrahepatic metastases, but in others their cause was uncertain and may have been related to the presence of hepatic metastases.

Fever, unaccompanied by infection and presumably due to neoplastic disease, was present in nineteen, or 23 per cent of the group. In six it was the major complaint that led to medical investigation. As a rule the fever was low grade in character, but in four instances the temperature ranged between 102° and 106°F. Night sweats were a prominent feature in four patients. As indicated in Table IV, the occurrence of fever was not peculiar to any one type of tumor. Eleven of the nineteen patients with fever had overt symptoms of liver disease, including hepatic pain in nine, a palpable mass in two, ascites in one and jaundice in two.

PHYSICAL FINDINGS

The principal physical findings are summarized in Table V.

Liver. On examination, 95 per cent of the patients exhibited one or more abnormalities of the liver. Hepatomegaly was the most common, the liver extending between 2 to 5 fingerbreadths below the right costal margin in forty-eight, and more than a handsbreadth in twenty-four of the eighty-one patients. Occasionally there was disproportionate enlargement of the left lobe. The liver could not be felt at all in four patients, and was palpable but not enlarged in five others.

Induration of the liver was present in sixty-two patients (77 per cent), including all those with palpable but normal-sized livers, and was described as hard in more than half the group. Occasionally, variations in consistency could be detected in different areas of the liver.

TABLE V
PHYSICAL FINDINGS IN EIGHTY-ONE PATIENTS WITH PROVED METASTATIC TUMOR OF THE LIVER

Abnormalities of the liver		77 (95%)
Enlargement	72 (89%)	
3–5 fingerbreadths	48	
>5 fingerbreadths	24	
Induration	62 (77%)	
Slight-moderate	28	
Marked	34	
Tenderness	52 (64%)	
Nodularity	43 (53%)	
Friction rub	8 (10%)	
Jaundice		22 (27%)
Mild to moderate (serum bilirubin <10 mg. per cent)	11	
Intense (serum bilirubin >10 mg. per cent)	11	
Ascites		25 (31%)
Signs suggestive of portal hypertension		26 (32%)
Splenomegaly alone	10 (12%)	
Splenomegaly plus prominent abdominal venous pattern	7 (9%)	
Prominent abdominal venous pattern alone	9 (11%)	
Other signs suggestive of advanced liver disease		16 (20%)
Spider angiomas	7 (9%)	
Palmar erythema	8 (10%)	
Gynecomastia	2 (2%)	
Flapping tremor	1 (1%)	
Fetor hepaticus	1 (1%)	

Hepatic tenderness was demonstrable in 64 per cent of the patients, including four of the five with palpable but normal-sized livers. In some, the tenderness was diffuse but in others it was localized, particularly over palpable metastatic nodules. Although the intensity varied considerably, exquisite sensitivity was common.

Nodules were palpable on the anterior surface or lower edge of the liver in 53 per cent of the patients. Many nodules were tender, or were associated with more generalized hepatic tenderness.

Eight patients (10 per cent) had an audible *friction rub*, which in two instances was also palpable. Typically the rub was heard over the anterior surface of the liver beneath the costal margin, but in two patients it was best heard over the anterior chest wall just above the right costal margin. Of those with a friction rub, seven had palpable hepatic nodules, five had marked hepatic tenderness and four had severe abdominal pain in the right upper quadrant.

As indicated in Table VI, hepatic pain, tenderness, induration, nodulation and friction rub were most frequent in those with the largest livers. In contrast, the occurrence of fever did not appear to bear any relationship to liver size, and hence to the degree of metastatic invasion, suggesting that the pyrexia may have been a manifestation of the primary tumor rather than of hepatic metastases.

Jaundice. Twenty-two patients (27 per cent) were clinically jaundiced. In eleven the presence of extrahepatic biliary obstruction was established by surgical exploration or necropsy, but in the remainder the cause of the jaundice was uncertain, although certain laboratory features suggested a biliary obstructive element in some and parenchymal destruction in others.

TABLE VI
CORRELATION BETWEEN LIVER SIZE AND MANIFESTATIONS OF HEPATIC METASTASES

Manifestations	No.	Hepatomegaly (%)		
		None (9 patients)	3–5 Fingerbreadths (48 patients)	>5 Fingerbreadths (24 patients)
Hepatic pain	29	11	25	67
Hepatic tenderness	52	44	60	83
Hepatic induration	62	56	70	100
Hepatic nodules	43	11	54	75
Hepatic friction rub	8	0	6	20
Ascites	25	33	33	25
Splenomegaly	17	22	23	16
Prominent abdominal venous pattern	16	0	16	33
Fever	19	22	23	25
Tumor demonstrable by initial biopsy	60	44	71	92

Ascites. Twenty-five patients (31 per cent) exhibited ascites. Tumor cells were demonstrated in the ascitic fluid in two, suggesting the presence of peritoneal tumor implants. Although others may have had similar metastases, portal hypertension, hypoalbuminemia and destruction of hepatic parenchyma, either alone or in combination, probably accounted for the ascites in many of the remaining patients, since eleven had prominent venous collaterals over the abdomen, seven had splenomegaly, twelve had serum albumin levels below 2.5 gm. per cent, eleven had edema and six had massive invasion of the liver by tumor.

In addition to the eleven patients with ascites and edema, there were eleven others with edema alone, so that a total of 44 per cent of the group had evidence of fluid retention. There was autopsy evidence of inferior vena cava occlusion by tumor in one patient. What role similar occlusion played in other patients with edema was not determined but the absence of venous collaterals over the legs and the presence of overt signs of liver disease and/or hypoalbuminemia suggested that these were the principal factors responsible for edema.

Signs Suggestive of Portal Hypertension. Twenty-six patients (32 per cent) had signs suggestive of portal hypertension, including splenomegaly, a prominent venous pattern over the abdomen or esophageal varices.

Splenomegaly was demonstrable in seventeen patients (21 per cent) and was accompanied by a prominent abdominal venous pattern in seven, ascites in seven and esophageal varices in two. The primary tumor in this group was located in the pancreas in eight and in a variety of sites in the remaining nine (breast three, lungs two, bile duct one and undetermined three).

Sixteen patients (20 per cent) exhibited a *prominent abdominal venous pattern* interpreted as evidence of raised portal pressure with an increase in portal-systemic collateral circulation. Of these seven had splenomegaly, twelve had ascites and one had esophageal varices. Since compression of the inferior vena cava by tumor was demonstrated at necropsy in one patient with pancreatic carcinoma, the possibility could not be excluded that it was present in some of the others and was responsible for the prominent abdominal venous pattern.

The two patients with splenomegaly who were examined postmortem had carcinoma of the pancreas with occlusion of the portal vein. That portal hypertension may have been due to intrahepatic rather than extrahepatic portal obstruction in many of the other patients is suggested by the fact that splenomegaly and a prominent abdominal venous pattern occurred predominantly in patients with significantly enlarged livers. (Table VI.)

Other Signs of Advanced Hepatocellular Disease. Seven patients (9 per cent) had spider angiomas, eight (10 per cent) had *palmar erythema* and two had *gynecomastia.* Whether these were attributable to the hepatic metastases or to associated malnutrition could not be determined, but the signs of advanced liver damage in these patients favored the former.

Signs of *hepatic coma* developed in two patients, including stupor and flapping tremor. In one there was fetor hepaticus, in the other the blood ammonia was increased. Postmortem examination revealed carcinoma of the pancreas with hepatic metastases and occlusion of the portal vein and inferior vena cava but no esophageal varices in one, and carcinoma of the breast with metastases to the liver but no evidence of portal obstruction or esophageal varices in the other.

LABORATORY FINDINGS

Anemia. Surprisingly few patients had severe anemia, only four showing packed red cell volumes of less than 30 per cent, or hemoglobin values of less than 9 gm. per cent. Thirty-five patients (43 per cent) had a packed red cell volume between 30 and 36 per cent, or a hemoglobin value of 9 to 12 gm. per cent.

Leukocytosis. Over half the patients (53 per cent) had significant leukocytosis, and of these more than a third had leukocyte counts in excess of 15,000 per cu. mm. High counts were no more common in those with fever (21 per cent) or hepatic pain (21 per cent) than in the remaining group.

Serum Bilirubin. In only 52 per cent of the group was the level of serum bilirubin elevated, and of these only half had values in excess of 4 mg. per cent and were clinically jaundiced. There was no correlation between the size of the liver and the level of serum bilirubin; indeed, in eight of the seventeen patients with massive hepatomegaly the level was normal.

Bromsulphalein Retention. Bromsulphalein retention proved to be a more sensitive index of hepatic dysfunction in patients with metastatic tumors of the liver than any of the other tests

employed, abnormal values being obtained in 96 per cent of the fifty-five patients tested, and in 95 per cent of the forty-four patients without clinical jaundice.

Serum Alkaline Phosphatase. Serum alkaline phosphatase levels were elevated in 82 per cent of the seventy-nine patients tested, and exceeded 20 units in half of the group. In the fifty-eight patients without clinical jaundice, the level was abnormally high in 78 per cent, and exceeded 20 units in 33 per cent.

Cephalin-Cholesterol Flocculation. Results of the Hanger test were positive in 41 per cent of the eighty patients tested, and in 36 per cent of the fifty-eight without clinical jaundice.

Thymol Turbidity. Increased values of thymol turbidity were found in 28 per cent of the seventy-eight patients tested, and in 16 per cent of the fifty-eight without overt jaundice.

Serum Proteins. The concentration of serum albumin was below 3 gm. per 100 ml. in 56 per cent, and below 2.5 gm. per 100 ml. in 33 per cent of the seventy-two patients tested. Serum globulin levels exceeded 4 gm. per 100 ml. in 31 per cent and 5 gm. per 100 ml. in 5 per cent of the patients.

Serum Glutamic Oxalacetic Transaminase. Serum glutamic oxalacetic transaminase activity was increased in 63 per cent of the twenty-four patients tested, three values exceeding 400 units (443, 506 and 539).

BIOPSY FINDINGS

Demonstration of Metastatic Tumor. Metastatic tumor was demonstrated in the liver by the *initial* needle biopsy in sixty of the eighty-one patients (74 per cent), and subsequently in two of six patients in whom biopsy was performed a second time and in one patient in whom a third biopsy was performed, so that the procedure ultimately was successful in establishing the diagnosis in 78 per cent of the group. In the eighteen failures, hepatic metastases were demonstrated by surgical exploration in twelve and by postmortem examination in six, usually within a month but not longer than six months after the initial needle biopsy.

As might be expected, the success of the needle biopsy in detecting tumor in the liver was dependent, in part at least, upon the extent of metastatic invasion, as reflected by the degree of hepatic enlargement. Thus, the *initial* biopsy specimen was positive in 44 per cent of the nine patients with no hepatomegaly, 71 per cent of the forty-eight patients with moderate hepatomegaly, and 92 per cent of the twenty-four patients with massive hepatomegaly. (Table VI.)

Table I illustrates the fact that hepatic metastases were demonstrable by the initial needle biopsy more often in patients with primary tumors drained by the systemic veins (89 per cent of twenty-seven patients) than in those with primary tumors drained by the portal vein (57 per cent of thirty-seven patients). This difference was statistically significant (chi square = 8.03, $p < 0.01$), and probably was related to the greater extent of the metastatic invasion of the liver in the former group. Thus, tumors drained by the systemic veins were accompanied by massive enlargement of the liver in 32 per cent and by normal-sized livers in none of the patients, whereas tumors drained by the portal vein were accompanied by massive enlargement of the liver in only 16 per cent and by normal-sized livers in 22 per cent of the patients. The possibility that the tumors drained by the systemic veins had a greater propensity for seeding the liver with metastases cannot be excluded. However, the fact that nine of the thirty-seven patients with tumors drained by the portal vein and none of the twenty-seven patients with tumors drained by systemic veins had proved extrahepatic biliary obstruction suggests that the former may have sought medical advice sooner because of jaundice, and hence had a shorter period in which to develop extensive hepatic metastases. Alternatively, the possibility must be considered that dissemination of tumor cells via the hepatic artery was more favorable than that via the portal vein for the implantation of neoplastic cells in the liver generally, or for the implantation of cells in the subcapsular area specifically where they were more accessible to the biopsy needle.

Only rarely was it possible to identify the source of the metastatic tumor, demonstrated by needle biopsy, on the basis of its histologic features alone. The six exceptions included two melanomas from the eye, two oat cell carcinomas and one epidermoid carcinoma from the lung, and one fibrosarcoma from the retroperitoneal space. In four other cases the demonstration of mucin-containing tumor cells was of value in directing attention to the gastrointestinal tract where the presence of a primary tumor was ultimately established.

Twenty of the needle biopsy specimens consisted of a solid core of neoplastic tissue, indicating their origin in metastatic nodules of macroscopic size. However, the remaining forty-three specimens contained both tumor and hepatic tissue, the former presenting as microscopic nodules and trabeculae invading the sinusoids, larger blood vessels or lymphatics. Taken together with the fact that a needle biopsy specimen usually represents approximately one fifty-thousandth of the total liver mass, this observation suggests that, by the time that metastatic nodules are evident, the liver usually is diffusely infiltrated by microscopic trabeculae of tumor tissue. This probably accounts for the remarkable frequency with which metastatic tumors can be demonstrated by random sampling with a small needle.

In two biopsy specimens routine sections yielded normal liver tissue, but serial sections of the same blocks revealed the presence of metastatic tumor.

Histologic Features of the Liver. In addition to the twenty-five biopsy specimens without tumor, forty-three of the sixty-three with tumor contained liver tissue suitable for histologic study. The most common finding in the portal triads of these sixty-eight sections was an inflammatory reaction (79 per cent). Often this was accompanied by periportal fibrosis (60 per cent). The portal involvement tended to be spotty in distribution, many of the triads being spared. In most sections the exudate was mononuclear in character, with occasional polymorphonuclear cells, but in those obtained from patients with extrahepatic biliary obstruction polymorphonuclear cells predominated, and usually the inflammatory reaction was more extensive.

The degree of periportal fibrosis varied, being graded as slight in 35 per cent and moderate in 25 per cent of the specimens. Two showed typical biliary cirrhosis, in one instance due to a carcinoma of the head of the pancreas, in the other to carcinoma of the common bile duct.

Proliferation of the perilobular bile ducts was evident in 31 per cent, but was moderate to marked in degree in only 9 per cent of the sections.

More than a third of the specimens (36 per cent) showed evidence of bile stasis, usually manifested by the presence of inspissated bile in dilated canaliculi; not infrequently larger collections of bile surrounded by pale foamy parenchymal cells in various stages of degeneration (so-called "bile infarcts") were found in the sections obtained from the patients with extrahepatic biliary obstruction. In three instances moderate to marked bile stasis was observed in patients with normal serum bilirubin levels, and in a fourth with a serum bilirubin concentration of only 3.1 mg. per cent.

Compression atrophy and necrosis of parenchymal cells bordering on tumor nodules and trabeculae were evident in all sections containing both liver and tumor tissue. Rarely the parenchyma was infarcted in an area adjacent to the tumor. Scattered areas of focal hepatitis unrelated to contiguous tumor masses were relatively common (39 per cent of the sections). Usually these were characterized by small circumscribed collections of mononuclear cells in the midst of which a few degenerating or necrotic parenchymal cells could occasionally be identified. Increased regenerative activity of the parenchyma was evident in 15 per cent of the specimens, manifested usually by the presence of many binucleate cells and thick parenchymal plates, and occasionally by mitotic figures and pseudoduct formation. Fatty infiltration of the parenchymal cells was present in half of the sections (45 per cent), but in only 12 per cent was it more than minimal in extent. Twenty-five per cent of the specimens showed varying degrees of sinusoidal congestion; particularly noteworthy was its patchy distribution.

In comparing the histologic features of the liver in sections with and without demonstrable tumor, no significant differences were noted. The presence of bile stasis in 57 per cent and a portal inflammatory reaction in 87 per cent of those without demonstrable tumor usually was interpreted as evidence of "probable biliary obstruction." In a few instances certain features aroused suspicion that a metastatic tumor was present but had escaped detection. These included periportal inflammation and bile stasis in the absence of jaundice, and the occurrence of significant congestion of the sinusoids, especially when patchy in distribution, in the absence of congestive failure.

Complications of Needle Biopsy. In no patient was biopsy performed unless the bleeding, clotting and prothrombin times were close to normal, and there was no history of abnormal bleeding in the skin or mucous membranes. In contrast to the experience of Fisher and Faloon [*2*], no serious complications of biopsy were encountered in this series. In two patients bleeding developed from the biopsy puncture wound, resulting in a subcutaneous hematoma in

TABLE VII

INITIAL DIAGNOSES SUGGESTED ON THE BASIS OF THE HISTORY AND PHYSICAL FINDINGS ALONE IN EIGHTY-ONE CASES OF METASTATIC TUMOR OF THE LIVER

Hepatobiliary disease		66 (81%)
Metastatic tumor of liver	53 (65%)	
Cirrhosis	5 (6%)	
Viral hepatitis	4 (5%)	
Common duct stone	3 (4%)	
Unclassified	1 (1%)	
Neoplastic disease		63 (78%)
Neoplasia with hepatic metastases	53 (65%)	
Neoplasia without hepatic metastases	8 (10%)	
Lymphoma	2 (2%)	
Other diagnostic possibilities		81 (100%)

TABLE VIII

PREBIOPSY DIAGNOSIS FOLLOWING COMPLETION OF LABORATORY AND OTHER DIAGNOSTIC PROCEDURES IN EIGHTY-ONE PATIENTS WITH METASTATIC TUMOR OF THE LIVER

Possibility of hepatic metastases considered		80 (99%)
Diagnosis considered most likely		
Metastatic tumor of liver		68 (84%)
Other diseases		13 (16%)
Cirrhosis	6 (7%)	
With hepatoma	4	
Common duct stone	3 (4%)	
Portal vein thrombosis	1 (1%)	
Amyloidosis	1 (1%)	
Brucellosis	1 (1%)	
Whipple's disease	1 (1%)	

one, and requiring local hemostatic measures in the other. None of the patients showed evidence of intraperitoneal or intrathoracic bleeding and none had signs of peritonitis.

DIAGNOSIS

Diagnosis before Biopsy. The diagnostic possibilities, based on the history and physical findings alone, suggested by the physician who examined these patients when they entered the hospital are summarized in Table VII. Multiple diagnoses were the rule, but the possibility of hepatic disease generally, or hepatic metastases specifically, was recognized in a high proportion of cases (81 and 65 per cent, respectively). This is not surprising considering the fact that all but one of the eighty-one patients had hepatic pain, ascites, jaundice, hepatomegaly or splenomegaly, either alone or in combination, clearly pointing to a disturbance in the liver. Similarly, the possibility of an underlying neoplasm was recognized in a high proportion of patients (78 per cent), since with few exceptions the patients had localizing signs or non-specific symptoms commonly associated with neoplastic disease. However, lest the erroneous conclusion be drawn from these data that the diagnosis of hepatic metastasis posed no problem in this series, it should be emphasized that in nearly every instance alternative diagnostic possibilities were given serious enough consideration to warrant time-consuming and often costly diagnostic procedures for their exclusion.

A more realistic appraisal of the problem may be gained from a consideration of the diagnoses recorded by the members of the Liver Study Unit just prior to biopsy and after most of the results of significant laboratory and other diagnostic procedures were available. It will be observed in Table VIII that metastatic tumor of the liver was considered possible in all but one of the patients, but was listed as the most likely diagnosis in only 84 per cent of the group. As might be expected, the enlargement and induration of the liver associated with signs of portal hypertension, fluid retention and/or spider angiomas were misinterpreted as evidence of cirrhosis in six of the thirteen patients diagnosed incorrectly; however, the malignant nature of the process was recognized in four of these, hepatoma being considered a complication. The combination of abdominal pain and obstructive jaundice suggested common duct stone in three and, for a variety of reasons that are self-evident, portal vein thrombosis, amyloidosis, brucellosis and Whipple's disease were considered most likely in one case each.

The diagnostic problem posed by the fever attributable to the primary tumor or its hepatic metastases in this series merits special comment. As previously indicated, six of the nineteen patients with such fever were admitted to the hospital because of "pyrexia of unknown origin." Four of these had been under treatment at home for several weeks, and had received antibiotic therapy without benefit. Although the possibility of neoplastic disease with metastatic spread to the liver was recognized during hospitalization in five of these patients, all but one were subjected to an exhaustive bacteriologic and roentgenologic study before the correct diagnosis was established by needle biopsy in four, surgical exploration in one, and necropsy in one. The paucity of findings pointing to the liver and the striking leukocytosis usually attributed to infection were the factors responsible

for the delay in recognizing the true nature of the disease in this group. Two patients illustrate the difficulties encountered.

In one patient with a striking daily remittent fever with temperatures of 102° to 104°F. associated with marked leukocytosis, hepatomegaly and roentgenographic evidence of pulmonary infiltrates, the initial diagnosis of metastatic carcinoma of the liver and lungs was abandoned because of a negative liver biopsy specimen and the finding of Cryptococcus neoformans in the sputum. Despite intensive antibiotic therapy the patient had a rapidly downhill course and died. Postmortem examination revealed carcinoma of the pancreas with pulmonary and hepatic metastases.

The other patient, a forty-three year old white woman, was admitted to the hospital because of persistent fever with temperatures up to 106°F. for four weeks. She had had no associated symptoms, but was known to be severely anemic. There was a history of exposure to brucellosis. Prior to admission she had failed to respond to a course of antibiotic therapy given for suspected subacute bacterial endocarditis. The initial diagnoses entertained at this hospital included brucellosis, tuberculosis, lymphoma and subacute bacterial endocarditis. Extensive bacteriologic and roentgenologic studies failed to disclose any abnormalities, and two liver biopsy specimens showed no evidence of tumor or granulomatous disease. A small mass in the neck, thought to be a lymph node, proved on biopsy to be a carotid body tumor. Since it appeared unlikely that this was responsible for the ferbile state, and since a trial of antituberculosis drug therapy had failed to affect the temperature, which continued to fluctuate between 104° and 106°F., exploratory laparotomy was carried out to exclude the presence of an unrecognized intra-abdominal abscess or tumor. The liver was found to be studded with numerous nodules, which on biopsy proved to be metastases from the carotid body tumor in the neck.

Diagnostic Value of Needle Biopsy of the Liver. Needle biopsy revealed the presence of tumor within the liver in 78 per cent of the patients studied. In 68 per cent the biopsy findings merely confirmed the diagnosis considered most likely before biopsy, but in 10 per cent they were critical in establishing the diagnosis when other possibilities appeared more likely. Although the biopsy specimen failed to demonstrate tumor in 22 per cent of the patients, the procedure proved to be of value in this group since it helped to exclude many of the other disorders of the liver under consideration. Thus the biopsy findings were deemed helpful in all but one of the eighty-one patients. In this patient, demonstration of granulomas in the biopsy specimen was misleading in that they were misinterpreted as evidence of "probable sarcoidosis."

COMMENT

All but one of the eighty-one patients with hepatic metastases described in this report had signs or symptoms referable to the liver. This is not surprising, considering that needle biopsy was a prerequisite for their inclusion in this series. Although the duration of symptoms in these patients was relatively brief, the ease with which the tumor was demonstrable by random sampling of the liver with a biopsy needle suggested that the lesions were widely disseminated. It is highly probable, therefore, that by the time localizing signs or symptoms appear in patients with hepatic metastases the disease is in an advanced stage of development.

It is apparent from this study that there is seldom any difficulty in recognizing that the liver is abnormal in patients with symptomatic hepatic metastases. However, the findings are seldom pathognomonic and are readily mistaken for signs of other disorders that affect the liver. Certain features of intrahepatic metastases deserve special emphasis. These include fever, a characteristic type of hepatic pain, signs of portal hypertension and the presence of a hepatic friction rub.

There was nothing characteristic about the fever in this group, but the fact that it was accompanied by leukocytosis and sweats often led to the erroneous impression that it was due to an infectious process. It is noteworthy, however, that even at its height the fever was never accompanied by shaking chills.

Considering the fact that more than a third of our patients had pain referable to the liver, and that in a quarter of the group it was the principal complaint, it is surprising that other authors either fail to mention pain or consider it an uncommon feature of metastatic disease of the liver [3]. Although the pain was never colicky, its intermittent sharp character not infrequently was misinterpreted as evidence of biliary colic; in several instances, because of its aggravation by respiration and cough, the pain was thought to be of pleuritic origin.

Portal hypertension is seldom considered a manifestation of hepatic metastases; yet almost

a third of our patients had splenomegaly, a prominent abdominal venous pattern or esophageal varices. It is well known that carcinoma of the pancreas may occlude the portal or splenic vein by direct extension [*4*], but in the present series only eight of the seventeen patients with splenomegaly had carcinoma of the pancreas, and in many of these, as previously indicated, there was suggestive evidence that the site of portal obstruction was intrahepatic rather than extrahepatic. Considering that Gullick [*4*] found splenomegaly in only three of his one hundred patients with carcinoma of the pancreas, it is remarkable that the spleen was enlarged in eight of our sixteen patients with carcinoma of the pancreas and in nine of the sixty-five patients with other types of tumor. Possibly this discrepancy is attributable to the special pains taken in all cases to establish whether or not splenomegaly was present. A prominent abdominal venous pattern was almost as common as splenomegaly, and in two patients esophageal varices were demonstrable. The latter are thought to be rare in patients with hepatic metastases, but Ruprecht and Kinney [*5*] encountered four cases in one year. Conceivably a systematic search for esophageal varices in such patients would reveal that the incidence is much higher than is generally recognized. Presumably the portal hypertension in patients with hepatic metastases is due to invasion, compression and distortion of the intrahepatic radicles of the portal vein by tumor. However, the fibrosis that often accompanies metastatic invasion and the peculiarities of the vasculature of intrahepatic tumors may be important contributing factors in some instances. Usually the desmoplastic reaction provoked by intrahepatic tumor is localized within and around discrete nodules, but occasionally it is diffuse and may produce a gross appearance indistinguishable from that of cirrhosis and may give rise to severe portal hypertension [*6*]. It has been shown that the blood supply of intrahepatic tumors is almost exclusively arterial [*7,8*] and that their main venous drainage is into the portal veins rather than the hepatic veins [*7*]. Accordingly, if the tumors are numerous the reflux of blood into portal system may be sufficient to raise the pressure.

The diagnostic importance of a friction rub over the liver has not received the emphasis it deserves. Although it has been reported in rare instances of cirrhosis [*9*] and in gonococcal perihepatitis [*10*], a friction rub over the liver is with rare exceptions pathognomonic of metastatic tumor in the liver. It was demonstrable in eight of our eighty-one patients and was helpful in establishing the diagnosis in every instance.

Of the tests commonly used to evaluate liver function, measurement of bromsulphalein excretion and the serum alkaline phosphatase level proved to be the most helpful in the differential diagnosis of hepatic metastases. Occasionally they suggested the diagnosis, but more often they lent support to a clinical impression based on other evidence. Although bromsulphalein retention was a highly sensitive index of hepatic dysfunction in this group, it was of little value in differentiating between metastatic tumor and other disorders of the liver. However, it was found with such regularity in proved cases (96 per cent), that often a normal value was helpful in excluding the diagnosis. The serum alkaline phosphatase level was less sensitive than the bromsulphalein test in detecting hepatic dysfunction in this group but had greater specificity, in that high values, especially those over 20 units, in the absence of hyperbilirubinemia or known bone disease, often suggested the possibility of an infiltrative disease of the liver, including metastatic tumor of the liver. A number of investigators [*11–13*] have emphasized the tendency of the serum alkaline phosphatase to rise, often to high levels, without a corresponding increase in serum bilirubin when the liver is infiltrated by tumor, granulomas or lymphoma.

The present study confirms previous reports [*14–16*] that needle biopsy of the liver is of great diagnostic value in patients with hepatic metastases. However, it should be recognized that the high degree of success achieved in demonstrating the presence of tumor both in this and other series is somewhat exaggerated, since the procedure usually is carried out in patients with overt manifestations of hepatic involvement who, as indicated previously, are in a late stage of their disease.

That needle biopsy of the liver entails a small risk is well documented [*17*]. Recently Fisher and Faloon [*2*] have warned against the special hazards of the procedure in patients with hepatic metastases, having encountered a mortality rate of 12 per cent in thirty-three cases. In contrast, there were no fatalities or serious complications in our own series of eighty-one cases, and Parets [*3*] in a review of his personal experience and that reported in the literature was unable to

find any evidence to support the view that the presence of hepatic metastases enhances the hazards of needle biopsy. It has been estimated that with due regard to accepted precautionary measures and contraindications the mortality rate of needle biopsy in the hands of experienced personnel is less than 1:1,000 [*17*]. This risk compares favorably with that of other widely used diagnostic procedures [*17*], and is probably less than that of exploratory laparotomy, although precise data on the risk in patients with hepatic metastases are not available.

At least a third of the patients in this series had primary tumors drained by the systemic veins, and in all but a few of these the metastases appeared to be confined to the liver. The tendency of metastases to localize in the liver irrespective of whether the primary tumor is drained by the portal or systemic veins has been emphasized by Cameron [*18*]. Environmental factors and the peculiarities of the circulation in the liver have been invoked as possible features responsible for the unusual susceptibility of the liver to metastatic invasion. Particularly difficult to understand is the paradoxical situation with respect to cirrhosis which, on the one hand, enhances the suspectibility of the liver to the development of primary hepatic tumors [*19*] and, on the other, appears to render the liver relatively immune to invasion by metastatic tumors [*20,21*].

SUMMARY

The clinical manifestations and needle biopsy findings in eighty-one patients with proved metastatic tumor of the liver have been reviewed. Attention is drawn to a number of insufficiently emphasized features of the disease that may be misleading. These include a characteristic type of hepatic pain, fever, signs of portal hypertension, fluid retention and the presence of a friction rub over the liver. Evidence is presented to show that once signs or symptoms of hepatic metastases appear, the disease is in an advanced stage of development, and that this accounts for the remarkable frequency with which the presence of tumor can be demonstrated by random sampling of the liver with a small biopsy needle.

The results of the present study confirm previous reports indicating the great diagnostic value of needle biopsy in metastatic disease of the liver, and support the view that the presence of hepatic metastases does not enhance the hazards of the procedure.

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Chronic Chlorpromazine Jaundice*

With Particular Reference to Its Relationship to Primary Biliary Cirrhosis

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JAUNDICE is a well recognised complication of therapy with chlorpromazine (Largactil,® Thorazine®) [*1–12*]. Occasionally the resulting icterus is prolonged and deep. Myers and co-workers [*13*] described a patient in whom xanthomas developed as part of this syndrome. After thirteen months this patient made a clinical recovery and a liver biopsy showed mainly portal fibrosis. We have found records in the literature of seventeen other patients in whom jaundice after chlorpromazine therapy lasted more than three months [*11,13–24*]; two of these showed skin xanthomas. (Table I.) A chronic obstructive-type jaundice with xanthomas has also been described by Chanutin and Ludewig [*25*] and by Stolzer and co-workers [*26*] as a complication of treatment with arsphenamine. The whole problem of cholestatic drug jaundice has recently been reviewed in an editorial by Gutman [*27*].

The purpose of this communication is to describe four patients with chronic cholestatic jaundice following chlorpromazine therapy, with special reference to the chemical abnormalities in the blood and to histologic changes in the liver. The relationship of the syndrome to primary biliary cirrhosis, which it can closely resemble clinically, is considered.

CASE REPORTS

CASE I. A twenty-eight year old woman, with vomiting of pregnancy, was given 75 mg. chlorpromazine daily for eight days. Administration of the drug was stopped when diarrhoea developed; one week later she became jaundiced. Because of the severity of the clinical picture it was decided to perform a laparotomy to exclude obstruction to the main bile ducts, but at operation no evidence of this could be found. Hepatosplenomegaly, however, was confirmed and a biopsy specimen was taken of the liver. Recovery from operation was uneventful but xanthomas began to appear on the skin of the back, elbows (Fig. 1), palmar creases and on the gum margins. (Fig. 2.)

Seven months after the beginning of her illness the patient was transferred to the Hammersmith Hospital. On examination, she was still deeply jaundiced, with widespread xanthomatosis, hepatosplenomegaly and evidence of weight loss. The serum bilirubin was 21.6 mg. per cent, serum cholesterol 1,120 mg. per cent and alkaline phosphatase 256 (King-Armstrong) units per cent. The result of both the thymol turbidity

TABLE I
PUBLISHED INSTANCES OF CHRONIC CHLORPROMAZINE JAUNDICE

Authors	Country	Sex	Duration (mo.)
Azima and Ogle [*16*]	Canada	?	7
Grytting [*17*]	Norway	M	6
Albacete et al. [*18*]	Cuba	F	9
Lemire and Mitchell [*19*]	U. S. A.	F	4
		F	4
Lomas et al. [*11*]	Great Britain	?	6
		F	3
Massachusetts General Hospital [*20*]	U. S. A.	F	3
Stacey et al. [*21*]	Canada	F†	7
Van Ommen and Brown [*22*]	U. S. A.	M	5
Myers et al. [*13*]	U. S. A.	M*	13
Brick and Buckley [*14*]	U. S. A.	M	4
		M	3
		F	5
Meyer and Cook [*23*]	U. S. A.	F	5
Gebhart et al. [*24*]	U. S. A.	M	10
		F†	10
Zelman [*15*]	U. S. A.	M	4
Read et al. [present series]	Great Britain	F†	36
		F	7
		F*	18
		F*	7

* Xanthomas.
† Pregnant.

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FIG. 1. Case I. Xanthomatous deposits on the elbow of a patient with prolonged chlorpromazine jaundice.



FIG. 2. Case I. Xanthomatous deposits on the gum margins of the same patient.

and the zinc sulphate tests was 1; the serum total proteins were 6.8 gm. per cent with 3.5 gm. albumin and 3.3 gm. globulin. Electrophoresis revealed an increase in the alpha$_2$ and beta-globulin fractions. The haemoglobin was 10.9 gm. per cent, white blood cells 10,000 per cu. mm., the mean corpuscular haemoglobin concentration was 30.5 per cent, and the prothrombin time fourteen (control twelve) seconds. Roentgenogram of the carpal bones taken seven months after the beginning of jaundice revealed some generalised thinning with cortical erosions suggestive of secondary hyperparathyroidism. (Fig. 3.) A barium series, apart from showing some distended ileal loops, was within normal limits.

Hepatic Histology. First biopsy specimen (surgical, after two months): There was some centrilobular bile retention but no evidence of a cellular reaction in the portal zones and no fibrosis. The liver cells looked normal.

Second biopsy specimen (after ten months): There was slight bile retention in the liver cells and occasional bile plugs were seen in the canaliculi. There was a great deal of bile in large, proliferated Kupffer cells and more still in phagocytes in the portal tracts. There were no signs of active liver cell damage but there were numerous foci of collapsed reticulum, devoid of liver cells and containing phagocytes, suggesting loss of groups of liver cells. The portal tracts were enlarged and irregular and often linked up with these foci. There was a slight infiltration of histiocytes, polymorpholeukocytes and lymphocytes. The striking change was the absence of bile duct epithelium—not one intact bile duct was seen, instead there were clusters of bile-stained phagocytes.

Third biopsy specimen (after fifteen months): There was little change from the previous biopsy. The amount and distribution of bile was about the same and the portal tracts were still enlarged and irregular but they had not become fibrosed. Several bile ducts now had a visible epithelium.

The subsequent course is summarized in Figure 4. Obstructive jaundice with pruritus and xanthomatosis persisted for thirty-six months. Now, after fifty-one months, the patient is free of jaundice but still has an elevated serum alkaline phosphatase level and fading xanthomas. The liver and spleen are slightly enlarged. Treatment with steroid drugs for three months (corticotrophin gel, 80 units daily, followed by prednisone, 45 mg. daily) did not affect the clinical course.

CASE II. A fifty-six year old woman was treated for depressive symptoms with 75 mg. chlorpromazine daily for four weeks. At the end of this time she had jaundice, with pale stools, dark urine and pruritus. She was transferred to another hospital because of deepening jaundice. A laparotomy was performed but no obstruction was found in the main bile ducts; an operative biopsy specimen of the liver was taken. Three months after the onset of jaundice she was transferred to the Hammersmith Hospital still jaundiced, with severe skin excoriation due to pruritus. The liver was enlarged and the spleen was palpable.

The serum bilirubin was 9.1 mg. per cent, the serum cholesterol 396 mg. per cent and serum alkaline phosphatase 68.3 (King-Armstrong) units per cent. The serum total proteins were 6.9 gm. per cent, 3.1 gm. albumin and 3.8 gm. globulin. Electrophoresis

showed an increase in the proportion of alpha$_2$ and beta-globulins. The haemoglobin was 11.4 gm. per cent, white blood cells 7,000 per cu. mm., the mean corpuscular haemoglobin concentration 29 per cent and prothrombin time thirteen (control twelve) seconds.

Hepatic Histology. First biopsy specimen (surgical, after three weeks): There was moderately severe biliary retention confined to the centrilobular regions. Most of the bile was in Kupffer cells but there were also plugs in canaliculi and in a few bile-stained liver cells, which appeared necrotic. The liver cells in the centrilobular parts showed "feathery" degeneration and contained hyaline deposits. There was apparent fatty change as fine vacuoles in scattered foci. There was evidence of liver cell regeneration in the centrilobular parts in the form of large nuclei and binucleate cells, but mitoses were not seen. The portal tracts were not enlarged and showed only a minimal infiltration with histiocytes and lymphocytes. The bile ducts nearly all showed an intact epithelium.

Second biopsy specimen (after three and a half months): Biliary retention was of about the same severity in this biopsy, showing a similar distribution but with a little more bile in the form of bile plugs. Evidence of liver cell damage had largely disappeared but a few degenerate and bile-stained cells were seen. There was still liver cell regeneration, including mitoses, but the infiltration of the portal tract was still mild.

After a period of seven months the jaundice faded, and recovery was complete. The serum cholesterol level rose to 1,050 mg. per cent and the highest serum bilirubin level recorded was 15 mg. per cent.

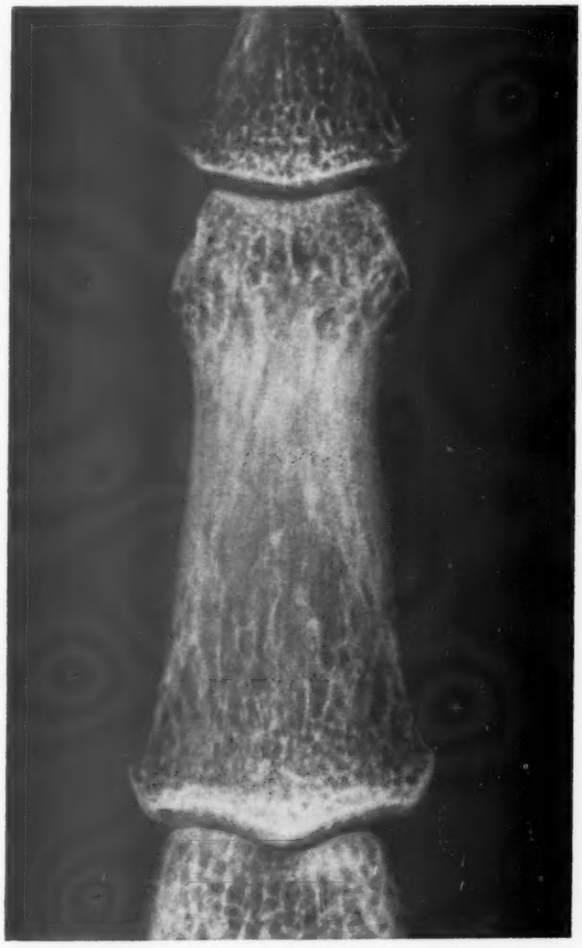


FIG. 3. Case I. Roentgenogram shows bone thinning and loss of subperiosteal bone in the carpus of the same patient, consistent with hyperparathyroidism.

CASE III. A fifty-seven year old woman was given 75 mg. chlorpromazine daily for two weeks for depression. A week after she stopped taking the tablets she had jaundice, with pale stools, dark urine and pruritus, and was admitted to the hospital. At operation no obstruction of the bile ducts could be found and a biopsy specimen of the liver was taken. Recovery from the operation was uneventful but the jaundice persisted and was accompanied by diarrhoea, weight loss and severe pruritus. On admission to the Hammersmith Hospital four and a half months after the onset of jaundice there was evidence of weight loss, deep jaundice, severe skin excoriation due to pruritus, and hepatomegaly.

The serum bilirubin was 11 mg. per cent, the serum cholesterol 1,640 mg. per cent, and serum alkaline phosphatase 106 (King-Armstrong) units per cent. The result of both the thymol turbidity and the zinc sulphate tests was 0, the serum total proteins were 6.4 gm. per cent, 3.5 gm. albumin and 2.9 gm. globulin. Electrophoresis showed an increase in the alpha$_2$ and beta-globulin components. The haemoglobin was 12.4 gm. per cent, the white cell count 8,000 per cu. mm. and the mean corpuscular haemoglobin concentration 33.5 per cent. The peripheral blood film showed macrocytosis. The barium series showed dilatation of the small bowel and x-ray examination of the hands showed some thinning of the carpal bones.

Hepatic Histology. First biopsy specimen (surgical, after three months): There was bile retention, mainly centrilobular and in the form of bile plugs in canaliculi and bile-filled Kupffer cells. There was a little bile in the liver cells. The liver cells showed damage in the form of "feathery" degeneration and there were hyaline deposits in a few. There were foci of liver cell loss with a polymorphonuclear and histiocyte infiltration. Many of the liver cells were binucleate and a few showed mitoses. Some of the portal tracts were moderately enlarged and irregular, being infiltrated by polymorphonuclears and histiocytes. In some of the tracts there were no bile ducts with an intact epithelium and only clusters of bile-stained phagocytes could be found.

Second biopsy specimen (after ten months): The biliary retention was minimal and comprised a few bile plugs, bile-filled Kupffer cells and bile phagocytes

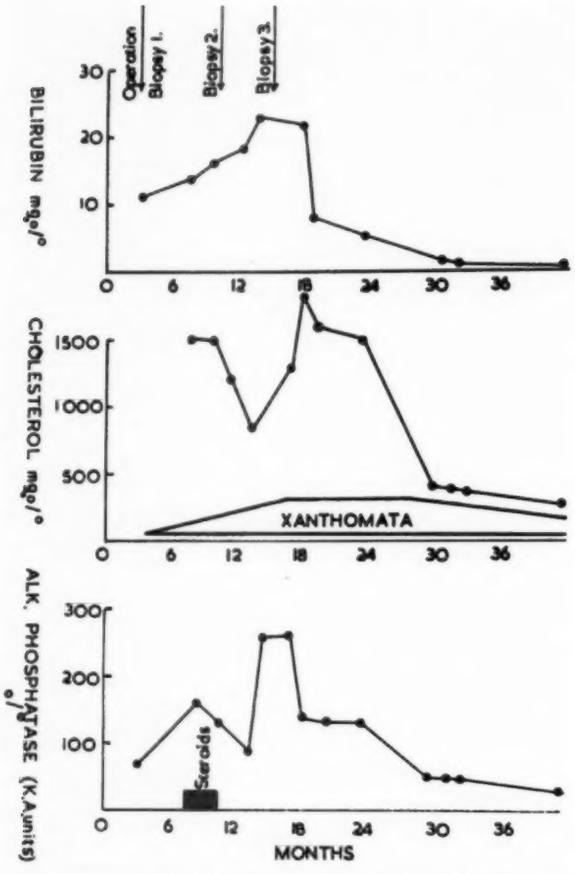


FIG. 4. Case 1. Clinical course of prolonged chlorpromazine jaundice.

in portal tracts. The liver cells were virtually normal and the portal tracts, although still infiltrated to about the same extent, now showed bile ducts with an intact epithelium.

Third biopsy specimen (after fifteen months): There was no evidence of liver cell damage or biliary retention in this biopsy specimen and the portal tracts, although still enlarged and infiltrated, showed no evidence of fibrosis.

This patient's jaundice lasted eighteen months and was accompanied by severe diarrhoea (14 pound weight loss) and pruritus. Xanthomas limited to the eyelids and palmar creases were present for five months and appeared seven months after the start of the jaundice. The serum bilirubin level has returned to normal but the alkaline phosphatase and serum cholesterol levels were still elevated (83 King-Armstrong units and 410 mg. per cent, respectively), twenty-seven months after the beginning of the illness.

CASE IV. A forty-two year old woman, depressed following the death of a relative, was given 75 mg. chlorpromazine daily for three weeks. Irritation of the skin and nausea developed two weeks later, and then jaundice, with pale stools and dark urine. A month later, because of deepening jaundice, a laparotomy was performed and no evidence of obstruction to major bile ducts was found; a biopsy specimen of the liver was taken. Six weeks later severe intestinal bleeding, presumably related to hypoprothrombinemia, necessitated a blood transfusion. The patient's general health remained good apart from loss of weight. A course of steroid drug therapy for two weeks (prednisone, 40 mg. daily, reducing to 20 mg. daily), had no effect on the jaundice and she was transferred to the Hammersmith Hospital for further investigtion three months after the onset of jaundice. On examination at that time there was deep jaundice, skin excoriation due to pruritus and evidence of weight loss. The liver was enlarged and palpable 3 fingerbreadths below the right costal margin.

The serum bilirubin was 12.9 mg. per cent, serum cholesterol 1,825 mg. per cent, and serum alkaline phosphatase 175 (King-Armstrong) units per cent. The result of the thymol turbidity test was 3, and of the zinc sulphate test 2; serum total proteins were 7.3 gm. per cent, 3.2 gm. albumin and 4.1 gm. globulin. Electrophoresis showed an increase in the $alpha_2$ and beta-globulin components. The haemoglobin was 8 gm. per cent, white cell count 8,000 per cu. mm. and mean corpuscular haemoglobin concentrations 31.5 per cent.

Hepatic Histology. First biopsy specimen (surgical, after one month) (Fig. 5 and 6): There was moderate centrilobular biliary retention, mainly in Kupffer cells, but also in the form of plugs in canaliculi and some in the liver cells. There was evidence of liver cell injury, the cells in the centrilobular areas often showing "feathery" degeneration and hyaline bodies; there was also concurrent evidence of liver cell regeneration throughout the whole section in the form of big nuclei, twin nuclei and mitoses. The portal tracts were not enlarged at this stage and showed only a minimal infiltration by lymphocytes and histiocytes.

Second biopsy specimen (after four months): This was essentially the same as the first biopsy specimen except that there were small foci of liver cell necrosis showing as clusters of small phagocytes enmeshed in collapsed reticulin. These foci lay mostly in relation to the portal tracts where bile duct epithelium was not visible.

Third biopsy specimen (after eleven months) (Fig. 7): Bile retention had not entirely disappeared and, apart from a few binuclear ones, the liver cells appeared normal. The portal tracts were now more enlarged than in the previous biopsy specimen and there was proliferation of bile ducts within them.

Fourth biopsy specimen (after eighteen months) (Fig. 8): Some of the portal tracts were still enlarged but much less so than in the last biopsy specimen and showing less cellular infiltration.

This patient's jaundice lasted seven months but the histologic changes were more prolonged. Xanthomas

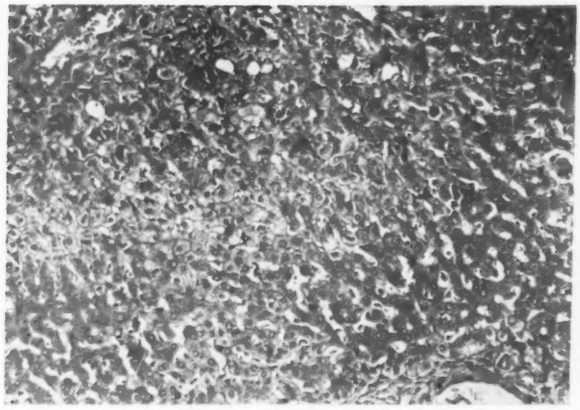


FIG. 5. Case IV. First biopsy specimen. Segment of a lobule with central vein top left and portal tract bottom right. Periportal cells appear relatively normal, centrilobular cells appear disorganised. Dark masses of bile visible in centrilobular half. Hematoxylin and eosin stain, original magnification × 132.

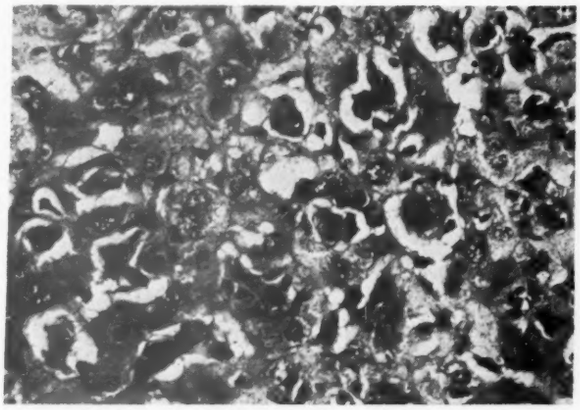


FIG. 6. Same biopsy specimen as in Figure 5. Centrilobular area. Bile thrombi in canaliculi show as black circles. Dark cells loose in sinuses are bile-laden Kupffer cells. Liver cells are swollen and show peripheral cytoplasmic vacuolation. Hematoxylin and eosin stain, original magnification × 410.

of the eyelids, cubital fossae and palmar creases developed as the jaundice faded, and they lasted four months. Pruritus of moderate severity, weight loss (35 pounds) and alimentary bleeding with chronic anaemia were also features of this patient's illness. Eighteen months after the beginning of the illness the alkaline phosphatase and serum cholesterol levels were still elevated (115 King-Armstrong units and 400 mg. per cent, respectively).

DIAGNOSIS

The clinical picture of a prodromal phase of anorexia, pyrexia and abdominal discomfort followed by an obstructive type of jaundice with pale stools, dark urine, and pruritus in patients taking chlorpromazine usually leads to prompt diagnosis. Difficulties arise in recognition when the patients present with the chronic, severe type of reaction we describe. Patients being treated with chlorpromazine often have neurotic disorders and may be taking many drugs, for such a person is very likely to consult more than one doctor. Much detective work may be needed to establish the true cause of "obstructive" jaundice in these patients. The routine practice of confronting the patient with likely tablets that cause jaundice is very useful. Patients with chlorpromazine jaundice may deny all knowledge of taking the drug; this was true of two of our patients. In these prolonged illnesses, the severity of the jaundice and the associated biochemical abnormalities may drive the clinician to a diagnosis of obstruction to major bile ducts

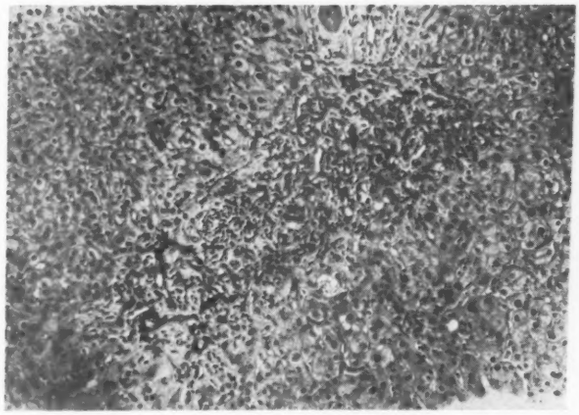


FIG. 7. Case IV. Biopsy specimen taken after eleven months. The portal tract is enlarged with irregular edges and contains proliferated bile ducts. Hematoxylin and eosin stain, original magnification × 122.

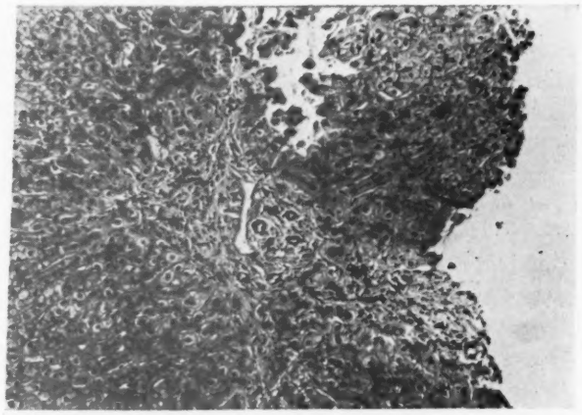


FIG. 8. Same case. Biopsy specimen taken after eighteen months. Portal tract has returned almost to normal. Hematoxylin and eosin stain, original magnification × 122.

and to early laparotomy. Recognition of this severe type of reaction to chlorpromazine is therefore important. In patients presenting with chronic obstructive jaundice due to chlorpromazine therapy there is also a risk that the duration of the jaundice may make the unsuspecting physician consider a drug aetiology unlikely. A search of the patient's drug cupboard at home is always rewarding [*14*].

Associated Clinical Findings (*Table I*). Xanthomatous deposits in the skin were seen in the three patients with the most prolonged jaundice, the lesions appearing within three to seven months of the onset of outset, and in two patients as the serum cholesterol level was returning towards normal. Extensive but continuously diminishing xanthomas are still present in the first patient after fifty-one months. This emphasizes the importance of duration of biliary obstruction as well as levels of serum cholesterol in their production.

Weight loss varying from 14 to 42 pounds was presumably related to steatorrhoea and to the anorexia accompanying a chronic illness. Serum albumin values fell, and in three of our patients reached levels below 3 gm. per cent. Anaemia was also a feature in three patients, in one patient it was clearly related to intestinal bleeding and a prolonged prothrombin time. The anaemia was less severe in the other two patients. Pruritus was a most troublesome symptom. Diarrhoea was marked in two patients with x-ray evidence in the barium series suggesting steatorrhoea. Two patients showed roentgenologic bone thinning presumably related to steatorrhoea. One patient (Case 1) had a raised value for the "wedged" hepatic vein pressure (15 to 20 mm. Hg) when investigated seven months after the onset of jaundice, showing that portal hypertension was present at this time.

Biochemical Features (*Table I*). All four patients showed a very striking rise in the serum values for alkaline phosphatase and cholesterol. The values for the serum cholesterol were above 1,000 mg. per cent in each case. In three patients, this level was achieved within three months of the onset and in the fourth this was noted when the patient was first seen by us after seven months of jaundice. Values as high as this are rare in extrahepatic biliary obstruction, and even in patients with chronic intrahepatic obstruction (primary biliary cirrhosis). In the patient studied by Myers and co-workers [*13*] the serum cholesterol level reached 2,500 mg. per cent. Studies with acetate-1-C^{14} showed increased cholesterol and phospholipid synthesis. Balfour [*28*] had previously noted, using P^{32}-labeled phospholipid, that the increased phospholipid level in obstructive jaundice due to blocking of the main ducts was related to overproduction by the liver rather than to the biliary obstruction or to decreased phospholipid breakdown by the tissues. The finding, in a patient with jaundice of short duration, of very high values for serum cholesterol and alkaline phosphatase strongly suggests a drug aetiology; in one of our patients it was this observation that led to the diagnosis of chlorpromazine jaundice. The serum bilirubin values were also elevated, ranging from 15 to 21.6 mg. per cent at their maximum.

HISTOLOGIC FEATURES IN THE LIVER

The Acute Case. For comparison with the chronic cases we will first describe the usual type of chlorpromazine jaundice. We have biopsy material from seven other patients with chlorpromazine jaundice of short duration. The changes are conveniently divided into bile retention, liver cell changes and portal tract reaction. *Biliary retention* was present in all seven, strictly centrizonal in six and generalized in one. Bile was present in liver cells and in Kupffer cells in all seven, and as plugs in the canaliculi in six. *Liver cell damage* was considerably less striking; two patients showed "feathery" degeneration [*29*] and fatty change and three patients had no recognisable evidence of liver cell damage apart from bile staining. One showed hyaline and fatty change, and three showed occasional points of liver cell necrosis with local cellular infiltration. However, all seven showed anisocytosis of liver cells and one showed mitoses. *The reaction in the portal tracts* was more constant; all but one patient had a polymorphonuclear and histiocyte infiltration and in one of these there was a heavy admixture of lymphocytes. Eosinophils were present in three and there was widening of the portal tracts in three with bile duct proliferation in one.

The differentiation of the picture of chlorpromazine jaundice from virus hepatitis is usually fairly easy but the differentiation from mechanical biliary obstruction may be more difficult. In general, bile retention is more severe in the mechanical group but the distribution of bile is similar. Liver cell damage tends to be more severe in the chlorpromazine group, in particular ballooned cells with peripheral

vacuolation and hyaline deposits within liver cells, although we have seen these changes in a few patients with mechanical obstruction. The portal areas are enlarged in both conditions, in chlorpromazine jaundice they often show only a mild infiltration of polymorphonuclears and histiocytes, in mechanical obstruction the reaction is heavier and polymorphonuclear.

The Chronic Case. The differentiation of the histologic features of prolonged chlorpromazine jaundice from those of primary biliary cirrhosis can be very difficult. One of our patients (Case II) showed no evidence of histologic progression, but in the other three the widened portal tracts with irregular edges gave the appearance of the aggressive infiltrating fibrosis seen in primary biliary cirrhosis. In two patients there was some bile duct proliferation. In the later stages the liver cell changes previously seen had mostly resolved and had, therefore, lost their diagnostic value. Biliary retention at this stage was not beyond that seen in primary biliary cirrhosis. In general, the resemblance to primary biliary cirrhosis was much greater than the differences. Two points of distinction emerged when the histologic features of our three patients with the most chronic cases were compared with those of eight patients with known primary biliary cirrhosis. In primary biliary cirrhosis the portal tracts were much more cellular and contained appreciable numbers of plasma cells, and in seven patients there was a high proportion of lymphocytes, with actual lymphoid foci in six. In the patients with chlorpromazine jaundice at a time when there was histologic resemblance to primary biliary cirrhosis, there was usually no residual liver cell damage, whereas in our patients with primary biliary cirrhosis, intralobular foci of liver cell destruction with local cellular infiltration were obvious. Another inconstant difference was the presence of "feathery" degeneration in the liver cells close to the fibrosed portal tracts; this was not seen in the patients with chronic chlorpromazine jaundice. Notwithstanding the differences, in most instances distinction is impossible unless the earlier stages are seen. The main differentiation would appear to lie in the degree of resolution which takes place in chronic chlorpromazine jaundice; this is particularly well illustrated by Case IV. The histologic appearances can progress to resemble those of primary biliary cirrhosis but even after a protracted clinical course the changes seem to be essentially reversible.

Management. Patients with prolonged jaundice often come to laparotomy, and all our four patients were operated upon. Usually no adverse effects ensue, but death has been reported after surgery [*30*] and, if possible, it should be avoided. Needle biopsy of the liver may help to distinguish between obstruction to bile ducts, which can be relieved by surgery, and that due to chlorpromazine. If the histologic picture is equivocal, a delay of three to four weeks allows time for improvement in the chlorpromazine cases and is not likely to affect the resectability of a malignant lesion of the pancreas or bile ducts which provides the most usual differential diagnostic problem. Serial biochemical determination may also reveal the very high serum cholesterol values suggestive of chlorpromazine jaundice.

Although little can be done to lessen the jaundice, complications can be prevented. In particular the administration of fat-soluble vitamins parenterally, particularly D and K, and calcium orally are important in preventing bleeding and bone thinning. A diet low in fat is useful in controlling diarrhoea, and norethandrolone, given for its antipruritic effect, may also be of value as an anabolic agent.

The most effective drugs for the treatment of pruritus due to biliary obstruction are methyltestosterone and norethandrolone (Nilevar®). Both can cause intrahepatic cholestasis and jaundice of similar type to that produced by chlorpromazine [*31,32*]. One might therefore be hesitant about their use in the treatment of chronic chlorpromazine jaundice. When used in primary biliary cirrhosis, there is invariably a rise in the serum bilirubin level [*33*]. Pruritus in two of our patients was so severe that small doses of norethandrolone were needed to relieve it. This did not seem to alter the tendency of the biochemical abnormalities to return to normal, although the effect on the total duration of the jaundice was of course unpredictable. Certainly norethandrolone was not responsible for the initial, characteristic biochemical abnormalities which we have described, which were present before it was prescribed. Zelman [*15*] used methyltestosterone to treat severe pruritus complicating chronic chlorpromazine jaundice and noted no untoward effects.

In the ordinary case of chlorpromazine jaundice a fall in serum bilirubin level when steroid therapy is given may coincide with a spontaneous remission. An effect observed during a

TABLE II
CLINICAL AND LABORATORY DATA IN THE PATIENTS STUDIED

Case No.	Age (yr.) and Sex	Indication for Chlorpromazine	Duration (mo.)		Maximum Serum Value			Xanthomas (+ − ++++)	Weight Loss (lb.)	Haemoglobin (gm./100 ml.)	Pruritus	Roentgenologic Evidence of Bone Thinning
			Jaundice	Biochemical Abnormality	Bilirubin (mg./100 ml.)	Alkaline Phosphatase (King-Armstrong units/100 ml.)	Cholesterol (mg./100 ml.)					
I	28,F	Vomiting of pregnancy	36	51+	21.6	256	1620	++++	42	10.9	++	+
II	56,F	Depression	7	?	15.0	68	1050	−	−	11.4	+	−
III	57,F	Depression	18	27+	18.5	290	1640	+	14	12.4	++	+
IV	42,F	Depression	7	18+	17.3	175	1825	+	35	8.0	+	−

prolonged period of jaundice would be more suggestive of a beneficial result of the drug. Neither of the two patients who received steroid therapy was less jaundiced at the end of treatment than at the beginning, and steroids could be dangerous in the presence of hypoprothrombinaemia producing intestinal bleeding. They may also increase the tendency to bone thinning and we do not believe, therefore, that steroids are indicated in the treatment of chronic chlorpromazine jaundice.

Prognosis. Eighteen other patients with jaundice due to chlorpromazine therapy, which lasted more than three months, are described in the literature. (Table II.) The course of the illness, with the exception of the case described by Myers et al. [*13*], has been, in general, less severe than in our four patients. Our first case has been unique, for jaundice persisted for thirty-six months. In every case reported in the literature, and in our cases, clinical recovery occurred even when xanthomatosis developed and despite the protracted course.

The chronic disease seems more common in women than in men. Two patients with prolonged jaundice took the drug during pregnancy; our patient with the most severe reaction was also pregnant. This apparent susceptibility may be related to the known occurrence of mild intrahepatic cholestatic jaundice in pregnancy, unrelated to the taking of drugs. This type is relieved by parturition and may recur with subsequent pregnancies [*34*].

The relationship between this disease and primary biliary cirrhosis must be discussed. Primary biliary cirrhosis is a disease of unknown aetiology [*35*], but the possibility that it represents a reaction to a drug or drugs such as chlorpromazine must be considered. Similarity between the clinical features of the two diseases is undoubted. The sex incidence and the secondary clinical and metabolic complications, pruritus, xanthomatosis, steatorrhoea and a haemorrhagic tendency are common to both. In the later stages of chlorpromazine jaundice, differentiation by physical examination and biochemical tests and without a history of the taking of the drug may be impossible. However, the patient with chronic chlorpromazine jaundice has a much more explosive onset, with a high initial serum bilirubin level followed by a slow fall with gradual disappearance of symptoms. Patients with primary biliary cirrhosis show a more insidious onset with mild or moder-

ate jaundice, the serum bilirubin level being maintained fairly constant for long periods of time with no return to normal. This difference is reflected in the more intense biochemical reaction at the outset seen in patients with chronic jaundice due to chlorpromazine therapy, the serum cholesterol and alkaline phosphatase values being much higher. The important difference is in prognosis. Even the most prolonged reaction to chlorpromazine, with obstructive jaundice for many months, has not so far been followed by an irreversible biliary cirrhosis. Our patient who was icteric for thirty-six months and in whom widespread xanthomas developed has shown a return to a virtually normal clinical stage. Recovery of a patient with primary biliary cirrhosis is unknown and to make this diagnosis is to give a death sentence. Patients with prolonged cholestasis due to the ingestion of drugs should not be labeled as suffering from biliary cirrhosis as there is no record as yet of such a sequence following jaundice due to the administration of chlorpromazine or other drugs such as neoarsphenamine and sulphadiazine [*36,37*].

The prognostic difference is reflected in the histologic changes seen in the liver in the two diseases. The picture resembles that of primary biliary cirrhosis most closely when the patient is recovering and when the jaundice and other clinical features are disappearing. These late and rather chronic histologic changes are no doubt reflected in the rather prolonged biochemical abnormalities seen [*38*]. We have shown, however, that histologic improvement, although lagging behind the clinical one, is followed by a return towards normal. An anatomic cirrhosis, with disorganization of the hepatic architecture, has never followed obstructive jaundice due to drug therapy.

The relationship between these two disorders is not as close as was suspected from their clinical similarity. It is of course surprising that intrahepatic obstruction of this duration should remit without permanent histologic damage to the liver. Our studies suggest that chronic chlorpromazine jaundice does not progress to "primary" biliary cirrhosis, the aetiology of which remains obscure. This statement must be qualified on various accounts. Clinical recovery has certainly ensued but, although there is no cirrhosis, a completely normal biopsy specimen of liver has not been seen. Moreover, the serum cholesterol and phosphatase values in our cases have also not yet achieved normality. A more definitive statement may be possible after a further period of follow-up.

SUMMARY

Four patients with chronic chlorpromazine jaundice are described, the icterus lasting seven to thirty-six months. The clinical picture was that of prolonged obstructive jaundice with steatorrhoea and weight loss. Three patients showed xanthomatosis. The biochemical changes included very high serum cholesterol and alkaline phosphatase values commencing early in the illness. The clinical picture may resemble that of primary biliary cirrhosis but the onset is more acute and a history of receiving the offending drug can be elicited.

In contrast to primary biliary cirrhosis, which is inevitably fatal, clinical recovery ensued in all four patients. Elevated serum alkaline phosphatase and cholesterol levels remained for many months after the jaundice had cleared. The histologic picture in the liver resembles that of primary biliary cirrhosis only in the later stages when clinical recovery is in progress. The portal zone infiltration and evidence of liver cell damage are always less in chronic chlorpromazine jaundice than in primary biliary cirrhosis. Although some changes persisted in the liver after clinical recovery, progression to the histologic picture of biliary cirrhosis was not seen.

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Aspirin and Gastrointestinal Bleeding*

Chromate^{51} Blood Loss Studies

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ASPIRIN ingestion has been shown to be associated in many normal subjects with occult gastrointestinal bleeding [*1–6*]. The pathogenesis of this phenomenon has not been fully elucidated. Hematologic abnormalities, changes in gastric secretion and erosive gastritis have been most frequently suggested as possible causes of the blood loss. Protection from gastrointestinal distress by taking aspirin with milk, food or antacids has been advocated, and the modification of occult bleeding by these measures also has been proposed.

The present study was designed to extend observations of intestinal blood loss following salicylate ingestion using a method of radiochromium tagging of red cells previously described from this laboratory [*6*].

PROCEDURE

One hundred forty-eight subjects were studied; they ranged in age from nineteen to eighty-three years. Eighty-nine were volunteer subjects, and fifty-eight were patients without known gastrointestinal disease. Radioactive chromium tagged red cells were injected and radioactivity of the stool was then measured to estimate intestinal blood loss.

Aspirin and other salicylates were administered for seven-day periods, interspersed with seven-day control periods when no drugs were taken. The order of the drug and control periods was varied to avoid artifacts that might be introduced by falling levels of blood radioactivity. In fifty-one of the volunteer subjects, periods of aspirin ingestion were both preceded and followed by control periods.

METHODS

Twenty to forty milliliters of the subject's blood was withdrawn, tagged with hexavalent sodium chromate^{51} in doses from 100 to 180 μc., and reinjected, according to the method described by Holt [*6*], assuring sufficient radioactivity in the blood for accurate measurements for approximately thirty days.

Fecal specimens were collected quantitatively in tared jars for four-day periods. A control period during which no drug was taken was used to rule out preexisting occult bleeding. Subjects took 600 mg. of aspirin, or an equivalent amount of another salicylate under study, a half hour before meals and at bed time for seven days. Stool specimens were collected beginning on the fourth day after the medication was started to allow for intestinal transit time. To study the accuracy of such experimental periods, daily stool estimations of radioactivity were made in four subjects. Fecal radioactivity appeared between the second and third day of ingestion of the medication and ceased about the second day of the succeeding period, indicating that blood loss began before and ended after the period of stool collection. In addition, it was noted that the daily excretion of radioactivity varied considerably, indicating the necessity for three- to four-day stool collections.

Stool specimens were homogenized and daily fecal blood loss calculated according to the procedure described in a previous communication from this laboratory [*6*]. The formula used for estimating fecal blood loss (F.B.L.) in terms of milliliters per day was:

$$\text{F.B.L.} = \frac{\text{total homogenate} \times \text{CPS of aliquot}}{\text{gm. of aliquot} \times \text{CPS of blood/ml.} \times \text{number of days}}$$

where CPS is counts per second of radioactivity [*6*]. Probabilities were estimated using the student test of "t" [*7*].

Prothrombin times, hemoglobin, white blood and differential counts, and salicylate levels were measured

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at appropriate stages in the study to assure against the inclusion of subjects with undiagnosed hematologic disease, and to document the presence of salicylates in the blood during the periods of salicylate administration.

Choline salicylate* was administered as a stable solution in a cherry flavored vehicle. Five milliliters of this solution contains 870 mg. of choline salicylate, equivalent in salicylate content to 650 mg. of acetylsalicylic acid according to the manufacturer [*8*]. Five milliliters of this solution was taken in 4 ounces of water four times daily. Calcium acetylsalicylate carbamide complex (subsequently referred to as calcium aspirin complex) was administered as tablets† each containing salicylate equivalent to 300 mg. of acetylsalicylic acid. Calcium aspirin complex has a solubility of 1 gm. in 5 ml. of water [*9*]. Aspirin‡ was administered in tablet form thirty minutes before each meal and at bed time in 117 subjects. Thirty-five subjects took aspirin previously crushed to powder form.

Eighteen cases in which the patients received anticoagulant therapy for myocardial infarction or thrombophlebitis were similarly studied, and are being reported in detail elsewhere [*10*]. Anticoagulation was achieved with acenocoumarin.§ One-stage prothrombin time determinations were measured six days a week and acenocoumarin dosage was adjusted accordingly to maintain the 12.5 per cent dilution prothrombin time between eighty and one hundred seconds.

RESULTS

Fecal excretion of radiochromium was measured in 148 subjects during a four-day control period during which stool specimens were collected; there was a mean daily blood loss of 0.5 ± 0.4 ml. per day.‖ One hundred eight subjects (73 per cent) lost more than 1.5 ml. of fecal blood per day during the standard reference period of aspirin ingestion. Only 3 of 148 subjects lost less blood during aspirin ingestion than during a control period. A daily blood loss of over 1.5 ml. (the mean plus 2.5 standard deviations) was considered significant, and subjects who lost less than this quantity of blood were labeled "non-susceptible."

Standard Aspirin Schedule. Occult fecal blood loss during periods of aspirin ingestion, 600 mg. four times daily, was measured in all the volunteer subjects and patients studied. The mean fecal blood loss on this regimen was 4.7 ± 4.1 ml. per day. This was considered the standard to which all other regimens were compared. Of all subjects studied, 73 per cent showed a significantly higher rate of bleeding during the periods of aspirin ingestion than during their own control periods. The mean fecal blood loss for this "susceptible" population was 5.1 ml. per day. Of the entire group studied 16 per cent (twenty-four subjects) bled more than 7 ml. per day, and 6 per cent (nine subjects) more than 10 ml. per day, the greatest quantity of blood lost being 90 ml. in a four-day period. These results are shown in Figure 1.

Age and Sex. The incidence of bleeding and quantity of blood lost were assessed in men and women in the age groups nineteen to thirty, thirty-one to fifty, and fifty-one to eighty-three years; these figures are summarized in Figure 2. The *incidence* varied little from the average of 73 per cent in the whole group. The *rate* of bleeding, however, was significantly higher in women aged nineteen to thirty, who showed a mean blood loss of 6 ml. per day, compared with a mean of 3.1 ml. in the remaining groups. No information is available to explain the increased susceptibility to aspirin-induced bleeding of these young women, most of whom were graduate nurses.

Dose Response. In order to compare the effects of varying doses of aspirin in the same subjects, thirteen subjects were given one, two or three tablets (300, 600 or 900 mg.) four times daily. The procedure was otherwise identical with that used during the standard schedule. Figure 3 shows that the mean fecal blood loss associated with these increasing doses of aspirin amounted to 4.6, 8 and 11.2 ml. per day, respectively.

These figures suggest a direct relationship between dose of aspirin and rate of fecal blood loss. Considerable individual variation in gastrointestinal bleeding was noted, however, as

* Choline salicylate was supplied as Arthropan® by the Purdue-Frederick Company, New York, New York.

† Calcium acetylsalicylate carbamide complex was provided as Calurin® by the Smith-Dorsey division of The Wander Company, Chicago, Illinois.

‡ The aspirin used in this study was taken from lots procured in bulk from Parke, Davis & Company. Aspirin supplied by E. R. Squibb & Sons was used in six subjects, and by Bayer in five subjects. "Buffered" acetylsalicylic acid (Bufferin®) was supplied by courtesy of the Bristol-Meyers Company. Aspirin enteric-coated to depend only on exposure time to moisture for disintegration was supplied by Eli Lilly & Company. The enteric coating includes stearic acid, carnauba wax, petrolatum, powdered agar and powdered elm bark.

§ Sintrom,® Geigy Pharmaceuticals, Ardsley, New York.

‖ The assumption that fecal radioactivity can be equated with fecal blood loss has been defended in a previous communication from this laboratory [*6*].

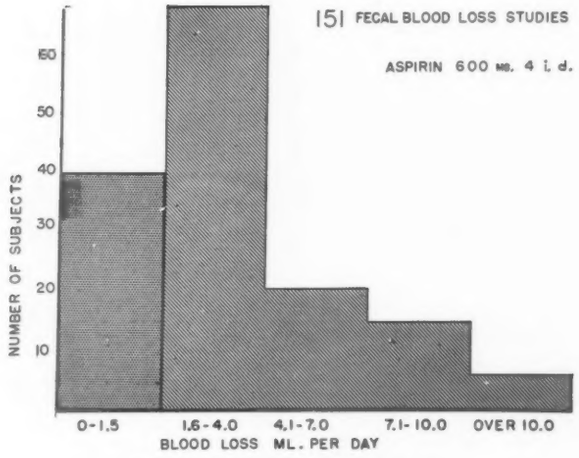


FIG. 1. Frequency distribution.

demonstrated by the high standard deviations; a stepwise increase in blood loss concomitant with increasing doses was found in only five volunteer subjects. Some subjects bled so extensively on a regimen of eight tablets a day that higher doses were not prescribed, while others failed to show significant bleeding on any dose.

Dose Frequency Study. Eight subjects took aspirin, one tablet (300 mg.) eight times per day, ingesting the same total dose (2.4 gm. a day) used for the aspirin reference period. In this group the mean fecal blood loss was 10.3 ml. per day, a highly significant increase from the aspirin reference period (600 mg. four times per day) blood loss in the same subjects ($P < 0.01$). One volunteer subject lost 12.7 ml. of blood per day while taking the identical dose in divided dosage every hour for sixteen hours. The results of this and all subsequent experiments are shown in Figure 4.

Crushed Aspirin. Thirty-five subjects took the standard dose of aspirin which had been previously crushed. The mean rate of bleeding was 4.7 ml. per day, a figure no different from that measured in subjects taking aspirin in tablet form.

Enteric-Coated Aspirin. The mean fecal blood loss associated with enteric-coated aspirin in eleven subjects was 3.6 ml. per day. The blood loss in the same subjects taking aspirin without enteric coating was 2.8 ml. per day. (Fig. 4.)

Aspirin with Food. In seven subjects 6 ounces of milk prescribed with two 300 mg. aspirin tablets four times daily did not protect against gastrointestinal bleeding; in this group the mean fecal blood loss was 4.9 ml. per day. Eight subjects took the aspirin tablets during three regular meals and with a supplemental evening meal; they lost an average of 5.1 ml. per day. (Fig. 4.)

AGE	NO. WOMEN	% BLEEDING	MEAN FECAL BLOOD LOSS	NO. MEN	% BLEEDING	MEAN FECAL BLOOD LOSS	ALL SUBJECTS	%BLEEDING	MEAN FECAL BLOOD LOSS
19-30	46	79%	6.0	40	74%	3.0	86	76%	4.6
31-50	18	55%	3.3	16	94%	4.6	34	72%	3.9
51-80	15	67%	2.1	17	67%	2.2	32	67%	2.2
TOTAL	79	71%	4.6	73	77%	3.2	152	73%	4.1

FIG. 2. Aspirin-induced bleeding. Age and sex distribution.

"Buffered" Aspirin. Eight subjects took a proprietary compound of acetylsalicylic acid with dihydroxy aluminum aminoacetate (approximately 40 mg.), and magnesium carbonate (approximately 100 mg.).* The mean fecal blood loss was 3.5 ml. per day, not significantly different from the aspirin-induced blood loss of 1.8 ml. per day in the same subjects. (Fig. 4.)

"Soluble" Salicylates. Two proprietary salicylate preparations specifically designed to provide greater solubility were compared with aspirin for effect on the rate of intestinal blood loss. Calcium acetylsalicylate carbamide complex (calcium aspirin complex) is readily soluble (1 gm. in 5 ml. of water) and liberates the acetylsalicylate radical. Choline salicylate is a solution

* Bufferin.

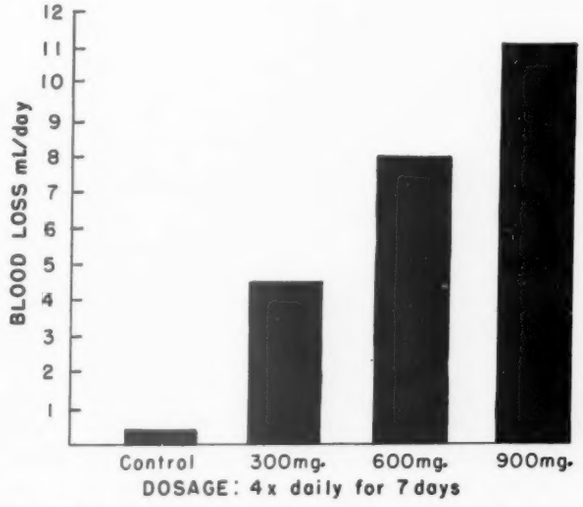


FIG. 3. Fecal blood loss with aspirin, response to varying doses and mean blood loss in thirteen volunteer subjects.

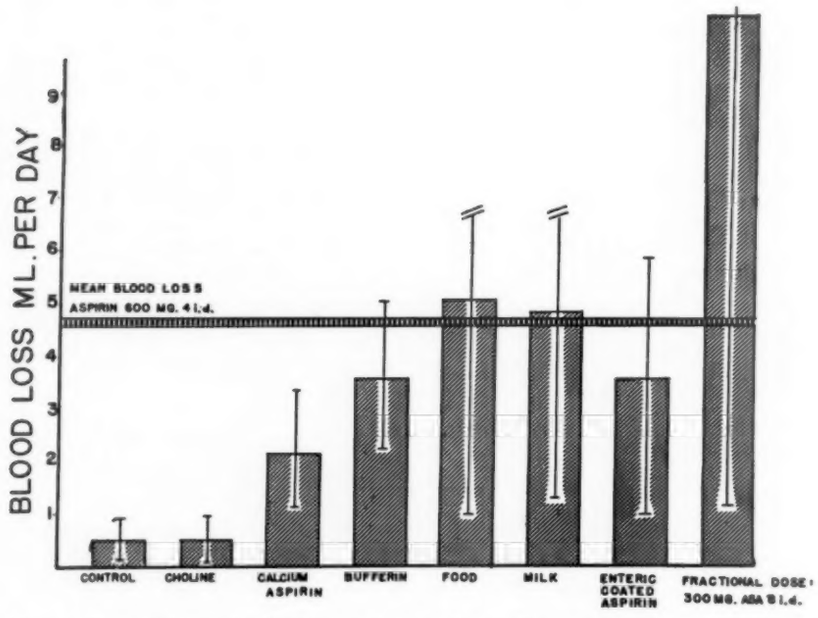


FIG. 4. Comparison of salicylate regimens. In studies represented by columns 2 to 7, 600 mg. (or salicylate equivalent) were taken four times daily.

administered as a liquid. Doses of the soluble salicylates were prescribed to provide equivalent levels of serum salicylate.

Calcium aspirin complex ingested as two tablets four times daily resulted in a mean fecal blood loss of 2.1 ml. per day in twenty-four subjects. The difference between this and the aspirin reference period blood loss is highly significant ($P < 0.01$). Twenty subjects had a mean loss of 0.5 ml. of fecal blood per day while taking choline salicylate. Thus occult fecal blood loss with this salicylate did not differ from that found during the control periods when no drug was taken. (Fig. 4.)

No attempt was made to compare different salicylates in respect to analgesia, serum salicylate levels or any other therapeutic end point. Evaluation of conflicting claims in this area was outside the scope of this study.

Hypoprothrombinemia. Seventeen patients receiving anticoagulant therapy were studied during control periods and during aspirin administration. The mean fecal blood loss during periods of good control of anticoagulation (12.5 per cent dilution prothrombin time between seventy-five and one hundred seconds) with acenocoumarin was 0.9 ml. per day. When aspirin in the standard dosage of 600 mg. four times a day was added to this regimen, a mean fecal blood loss of 5 ml. per day was noted. There was no significant difference between these figures and those for normal volunteer subjects [*10*].

COMMENTS

The occasional association of aspirin ingestion with massive gastrointestinal bleeding has been known for many years; however, the frequent occurrence of occult blood loss during administration of pharmacologic doses of the drug has been established only recently. The method herein employed, of chromium[51] labeling of red cells and detection of radioactivity in the stools, appears to be the most accurate available to quantify such bleeding under varying conditions.

Hypoprothrombinemia secondary to aspirin ingestion seems to be excluded as a significant cause of aspirin-induced intestinal bleeding. Salicylate-induced changes in prothrombin level were minor over the short period of observation, and subjects in this study who took aspirin while their serum prothrombin levels were lowered by anticoagulant therapy bled no more than normal volunteer subjects.

The theory of aspirin-induced erosive gastritis has gained much acceptance. The evidence on which this theory is based includes gastroscopic demonstration of hyperemia and bleeding around aspirin particles [*2*], demonstration of acute ulceration beneath aspirin fragments in

gastrectomy specimens [*3*], and histologic alteration in gastric biopsy specimens taken after aspirin ingestion [*11*]. When the erosion theory is examined in the light of our data, certain inconsistencies appear. The ability of aspirin directly to injure the gastric mucosa might be dependent upon close contact of insoluble particles of the drug for some time, especially if these particles became embedded in folds of mucosa. One might have expected, therefore, that changes in the particulate size of the preparation administered, by crushing and powdering, would diminish significantly the number of such erosions and subsequently reduce blood loss. In addition, concomitant administration of food or milk might reduce the mucosal exposure to undissolved fragments. We have demonstrated, however, that these procedures do not affect gastrointestinal bleeding as measured by the radiochromium technic. While a simple erosive process is not thereby excluded, the existence of other mechanisms is suggested. The data showing that enteric coating does not prevent bleeding also indicates that the gastric mucosa may not be the only susceptible site.

The possibility that aspirin-induced gastrointestinal bleeding is related to the insolubility of acetylsalicylic acid has been suggested in recent studies of the physicochemical constants of various aspirin tablet preparations [*12*]. Aspirin is relatively insoluble, requiring 300 parts of water for solution. Calcium acetylsalicylate carbamide complex was used in these studies as this drug resembles aspirin in providing the acetylsalicylate molecule in the plasma,* but has a greater solubility (1 gm. in 5 ml. of water at 25°c). Clinical studies suggest that acetylsalicylic acid may possibly have greater analgesic properties than sodium salicylate [*13–15*]; conceivably this effect could be ascribed to the alleged circulation of acetylsalicylate molecules unbound to plasma protein for thirty to sixty minutes before complete hydrolysis and subsequent protein binding [*15,16*]. The acetyl group is not essential, however, for therapeutic action, as relief of pain, inflammation and fever are obtained when adequate doses of sodium salicylate are prescribed [*15*].

The results of our investigations with calcium aspirin complex showed that significant intestinal bleeding was produced, but that the quantities lost were less than when ordinary aspirin preparations were administered to the same subjects. The calcium and other inert excipients* in the calcium aspirin complex tablets are unlikely to have been responsible for the reduction in bleeding since no additives were discovered to affect the blood loss associated with the ingestion of aspirin tablets. This evidence suggests that the solubility of a salicylate product may influence the rate of bleeding. However, as *some* alimentary blood loss still did occur, despite the solubility of the calcium aspirin preparation, other factors may be involved.

Exhaustive dispersion studies of aspirin tablets at many ranges of pH, temperature and concentration gradient have shown that dissolution is minimally dependent on the concentration of aspirin already in solution, within the therapeutic dose range [*17*]. A given fraction of a tablet dissolved in a constant fraction of the total dissolution time almost independently of pH and temperature. Stated differently, in half the total dissolution time the amount in solution was always between 88 and 89 per cent of the total weight. Half the tablet was dissolved in 18 to 20 per cent of the total dissolution time. Recent studies by Levy and Hayes [*12*] have again indicated that the rate-limiting factor in the time of salicylate absorption depends on the physicochemical properties of tablet dissolution.

Administration of aspirin tablets four times daily to the same subjects in doses ranging from 1.2 to 3.6 gm. a day established a relationship between quantity of blood lost and dosage used. A sharp increase in rate of bleeding was noted when the standard dosage of 2.4 gm. a day was taken in eight or sixteen fractions each day instead of the usual four divided doses. Only wholly dispersed and dissolved particles can cross the intestinal mucosa, and the total *number* of aspirin particles to which the mucosa is exposed is presumably identical when the same dose is taken. The dispersion time of 150, 300, 600 and 900 mg. in the form of 150 and 300 mg. tablets does not differ greatly so that a single dose of any size will be absorbed in approximately the same time. Therefore when *administration* is more frequent, irrespective of change in dose, the total time during which the intestine is exposed to undissolved aspirin particles is greater.

* Whether calcium aspirin complex is hydrolysed to acetylsalicylic acid, calcium and urea by intestinal enzymes prior to absorption, or is so hydrolysed in the blood stream, is not known.

* Starch, lactose and magnesium stearate.

These facts suggest that the blood loss is related not only to the solubility of the preparation but also to the size of the dose and the frequency of administration. Of these variables, changes in the frequency of administration resulted in the greatest changes in rate of bleeding.

The administration of choline salicylate was unrelated to intestinal bleeding in this study; enteric-coated sodium salicylate has also been shown to be free of this complication by other workers [*1,18*]. Both drugs are highly soluble in water and, as previously discussed, solubility does influence rate of bleeding. However, subjects taking calcium aspirin complex still lost significant amounts of blood despite the greater *in vitro* solubility of this compound. The main pharmacologic difference between these compounds lies in acetylation; choline salicylate and sodium salicylate lack the acetyl radical which is maintained in the calcium aspirin complex. It may be argued, therefore, that the presence of the acetyl group on the salicylic acid molecule is a factor in the induction of gastrointestinal bleeding.

Site of Bleeding. The gastric mucosa has been demonstrated to be susceptible to the hemorrhagic effect of aspirin by many observers [*2,3,11*]. Enteric-coated aspirin ingestion* induced a similar rate of bleeding in this study, implicating the small intestinal mucosa as an additional susceptible site.

Individual Susceptibility. Individual susceptibility to aspirin-induced bleeding is highly variable. It is of interest that in a number of recent studies it has been discovered that approximately 70 per cent of subjects are susceptible, regardless of the method of study or the population studied [*1,4*]. Division of the study population by age and sex shows that young women in this investigation were significantly more susceptible than other groups in regards to the rate of aspirin-induced bleeding. In individual instances the blood loss could not be predicted in advance; some young women did not bleed on any regimen, whereas some elderly men from the least susceptible age group lost considerable amounts of blood. Some subjects lost a quite consistent quantity of blood when a dosage regimen was repeated.

Significance of Blood Loss. Prolonged daily blood losses of 5 ml. in a menstruating woman could deplete iron reserves at a significant rate, if iron absorption were unchanged [*19*]. The same rate of blood loss in a man would also produce a negative iron balance. That aspirin may induce a continuous blood loss during a period of many months has been demonstrated by Stubbé [*1*] in long-term studies using fecal benzidine tests. However, knowledge of the homeostatic mechanisms of iron absorption is too incomplete to deduce from this fact that chronic aspirin ingestion might induce iron deficiency anemia. It is probable that much of the iron lost in bleeding of the upper intestinal tract is available for reabsorption in the more distal intestine; such reabsorption is suggested by studies of anemic patients with heavy hookworm infestation in whom iron reabsorption was found proportional to the degree of anemia [*20*]. Much has been written on "aspirin anemia" [*21*]; evaluation of the clinical importance of this entity awaits completion of critical long-term studies capable of measuring iron distribution, for which the technics are now at hand.

* The ability of the enteric coating to pass the pylorus was not tested. Achievement of appropriate blood salicylate levels in all subjects taking enteric-coated aspirin, and absence of any tablets in the four-day fecal collection, showed that the material was absorbed.

SUMMARY AND CONCLUSIONS

Aspirin-induced gastrointestinal bleeding was measured in a group of 148 adult patients and volunteer subjects of both sexes using a method of chromate^{51} tagging of red cells.

Seventy-three per cent of subjects bled significantly. The quantity of blood lost was related to total dose of aspirin taken and to frequency of administration. Variations in individual susceptibility to aspirin-induced bleeding varied; degree of susceptibility could not be predicted by age or sex.

Ingestion of tablets which are enteric-coated did not significantly influence the rate of bleeding nor did hypoprothrombinemia, or concomitant ingestion of milk or food.

A relatively soluble salicylate (calcium aspirin complex) produced less bleeding than did various preparations of aspirin. One soluble nonacetylated salicylate (choline salicylate) was not associated with intestinal bleeding.

The mechanism of alimentary blood loss following aspirin ingestion is not known. The possible importance of dissolution characteristics, solubility and acetylation is discussed.

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Aspirin and Gastric Bleeding*

Gastroscopic Observations, with Review of Literature

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THE universal popularity enjoyed by acetylsalicylic acid as an effective antirheumatic and analgesic agent, coupled with its ready availability in countless proprietary medicines, prompts the need for critical evaluation of any gastric irritation which might be induced in the usual therapeutic doses. Despite numerous studies in the past designed to elucidate the precise role, if any, played by aspirin in the causation of gastric hemorrhage, conclusions remain contradictory.

Long before any means were available to test the notion objectively, salicylates were suspected of exerting an injurious influence on gastric function [*1*]. This impression was based largely on common clinical experience with patients who reacted unfavorably to the oral ingestion of salicylates, with epigastric distress, heartburn, nausea and vomiting; later, experimental observations [*2*] enlarged upon this phase of salicylate toxicity. However, a much more serious implication is the relationship of this drug to gastroduodenal hemorrhage. This aspect of the problem has been investigated by a variety of methods, namely, statistical analysis of clinical data [*3,8*], analysis of gastric aspirations for blood [*8,9*], studies of the incidence of positive stool guaiac tests after the administration of aspirin [*5,10*], and direct gastroscopic observation [*11,16*].

Information gathered from gastroscopic study is particularly relevant since it permits direct visualization and recording of any vascular or erosive change induced by aspirin. In 1938 Douthwaite and Lintott [*11*], the first observers to utilize the gastroscope for this purpose, contended that aspirin had a direct irritative effect on the gastric mucosa, causing capillary and mucosal injury with bleeding and erosions. On gastroscopic examination 80 per cent of their group of sixteen patients to whom 15 gr. of aspirin was administered showed varying degrees of hyperemia, submucous hemorrhage and ulcerative change. Paul [*13*], in a later important gastroscopic study, came to a diametrically opposite conclusion. No vascular or hemorrhagic change or other evidence of acute gastritis was encountered in patients with both functional and organic gastric disease after single or repeated doses of aspirin given prior to gastroscopy. He concluded that "aspirin does not produce hyperemia or hemorrhage in the gastric mucosa." Similarly, Caravati and Cosgrove [*15*], in an experimental investigation designed to pinpoint the precise locus of the emetic action of sodium salicylate, failed to elicit any erosive or hemorrhagic change in the gastric mucosa. Their gastroscopic studies were performed after oral as well as intravenous administration of sodium salicylate, and in only one patient was "minimal gastritis" observed. Wolf and Wolff [*17*] also were unable to produce bleeding or an erosive lesion by direct application of aspirin to the mucosa of a patient with gastrostomy. This question would seem, therefore, to have been settled were it not for compelling evidence in more recent publications by Muir and Cossar [*8,18*], Kelly [*19*], and Schneider [*9*] which once more raised suspicion of the irritant potentialities of aspirin.

Critical review of the former gastroscopic studies raises a reasonable doubt as to justification of the conclusions drawn due to failure to obtain control comparative examinations. None of the previous workers compared the state of the gastric mucosa before and after the administration of aspirin. Douthwaite [*11,16*] recognized this objection but disposed of it as a theoretical consideration. However, clinical experience with numerous diagnostic gastros-

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copies has repeatedly taught us that minor vascular changes, such as submucous hemorrhages, patchy transitory hyperemia, petechiae, and even minute erosions are often found even when no presumptive gastric irritant has been taken. Therefore control examinations are a necessary preliminary to the collection of acceptable data on this question. In the light of these considerations, an investigation was undertaken to ascertain by gastroscopic observation the immediate effect of single doses (0.6 to 1.6 gm.) of acetylsalicylic acid on the gastric mucosa, each subject serving as his own control.

A brief review and evaluation of the experimental findings of previous investigators will first be presented.

REVIEW OF LITERATURE

Broadly speaking, two chief types of gastric intolerance reactions have been described: (1) a subjective symptom complex comprising epigastric discomfort, abdominal cramps, heartburn, nausea and vomiting; and (2) an inflammatory reaction including congestion, hemorrhage, erosion and ulceration.

With respect to the first type of reaction, the symptoms were attributed by Schnedorf and co-workers [*2*] to a depression of gastric motility and a stimulant action on acid secretion. Experimentally, in both human subjects and animals, they obtained objective evidence of a delay in stomach emptying when aspirin was administered in single doses through a gastric tube. Repeated administration of the drug for a short period of three days in doses of 3 gm. per day induced vomiting in many of their experimental animals. It was concluded that these symptoms were the direct consequence of a reduced gastric emptying rate. An increase in titratable acidity was obtained by these investigators with single and repeated doses of aspirin, although it is doubtful whether their reported 17 per cent increase can be considered significant. These effects were ascribed to a direct local action on the stomach.

The divergent opinion regarding the locus of action of aspirin expressed recently in a popular textbook of pharmacology and therapeutics [*20*] is probably based on the work of Caravati and Cosgrove [*15*]. These latter investigators, in a study of the vomiting induced by salicylates, obtained an emetic effect after administering the drug intravenously, before any salicylic acid could be detected in the gastric secretion. Therefore, they concluded that nausea and vomiting were caused by a central action and not by a direct effect on the stomach peripherally. Incidentally, they could not confirm the stimulant action of salicylates on acid secretion, when the drug was administered either intravenously or orally. The gastroscopic portion of their study will be discussed later in relation to our own findings.

Batterman [*21*] in a recent report noted symptoms of gastrointestinal intolerance in 8 to 10 per cent of subjects taking aspirin for a single day and in 17 to 20 per cent of those receiving the drug for periods up to several weeks.

The second type of gastrointestinal reaction to aspirin, i.e., congestion, hemorrhage and erosion, is important clinically since it may provide the clue to hitherto obscure cases of gastrointestinal bleeding. Autopsy studies in cases of salicylate poisoning [*22*] disclose marked morphologic changes in the gastrointestinal tract, including congestion, edema and hemorrhage into the mucous membranes. In view of the profound physiologic disturbances involving the respiratory center, fluid balance, cardiac dynamics and acid-base equilibrium which occur in salicylate poisoning, it seems likely that these physiologic effects, rather than the local action of the salicylates *per se*, are the direct cause for the pathologic changes noted in the digestive tract.

Numerous animal experiments attest to the ulcerogenic action of salicylates. Gastric ulceration was found by Schnedorf [*2*] at autopsy in two-thirds of the dogs given aspirin for several weeks. Barbour and Dickerson [*23*] produced gastric ulceration in experimental animals with acetylsalicylic acid administered hypodermically. Bleeding into the pouch of Cope-pouch dogs was observed by Clark and Adams [*24*] when aspirin was administered in doses of 140 and 190 mg. per kg. daily for five days. Marked gastric irritant effects were also produced in rats by Seeberg et al. [*25*] with acetylsalicylic acid. At autopsy their rats showed hyperemia, areas of hemorrhage, erosions and ulceration in the fundus and lesser curvature of the stomach with single doses of 100 mg. per kg.—a single dose level somewhat higher than that used in clinical therapeutics. Goodman and Gilman [*26*] also report the production of gastric ulceration in experimental animals by the administration of large doses of salicylates. Sollman [*20*] states that "large doses of acetylsalicylic acid (150 mg. per kg. of body

weight by mouth or 300 mg. per day hypodermically) produce mucosal ulcers of the stomach in rats."

On the clinical side, the literature abounds in reports of patients who have had repeated bleeding episodes of baffling origin, in whom careful studies led to a strong presumption that aspirin was the offending agent. Hurst's patient [*12*], a migraine sufferer, took six to forty-two tablets of aspirin weekly for years, usually uncrushed and without water. Multiple episodes of gross upper gastrointestinal bleeding and a slow constant ooze over many years led to prolonged weakness and anemia. Gastroscopic examination after the ingestion of two tablets of aspirin showed marked hemorrhagic changes in the gastric mucosa. The patient's clinical condition was corrected after the administration of aspirin was discontinued. Kelly [*19*] cites three case reports of highly suspicious aspirin-induced bleeding. Four patients with bleeding presumed to be caused by the ingestion of aspirin, in whom clinical and x-ray studies revealed no other source of hemorrhage, are described by Waterson [*3*]. Previous intolerance reactions such as retrosternal pain, heartburn, nausea and vomiting after the intake of aspirin were reported by each patient. A carefully documented patient is one observed by Modell [*27*] for obscure gastrointestinal bleeding of seven years' duration, manifested by repeated melena and constantly positive stool guaiac tests, and iron deficiency anemia. Although a rectal polyp and carcinoma of the colon were found and removed, and a hiatus hernia was evident on roentgenogram, the bleeding did not stop until the patient ceased taking aspirin, which he had formerly consumed in amounts of 3 gm. daily. Intestinal bleeding ceased whenever the aspirin was discontinued and recurred when the drug was readministered. Blood coagulation studies revealed no hypoprothrombinemia or other impairment of the clotting mechanism. Six months follow-up without aspirin disclosed no further gross or occult bleeding and the hemoglobin remained normal. The extent of the gastroduodenal bleeding initiated by aspirin in such patients would presuppose a concomitant erosive and ulcerogenic action. Indeed, acute erosive gastritis was the lesion produced in the patients to whom Muir [*8*] administered test doses of aspirin prior to undergoing subtotal gastrectomy. Lange [*5*] also reported a significant association between aspirin ingestion and acute erosive gastritis.

Statistical surveys have provided somewhat conflicting evidence on this question of aspirin bleeding. In 1956 Brown and Mitchell [*4*] studied the relationship of the ingestion of salicylates and alcohol to the onset of gastrointestinal bleeding in Negro patients with proved peptic ulcer disease. Seventy per cent of a group of forty-six patients ingested varying doses of salicylate drugs just prior to the onset of hemorrhage. In a group of one hundred control patients without ulcers, the incidence of aspirin ingestion was 40 per cent. This difference was considered to be statistically significant. A similar analysis of nine patients with perforated ulcer is rather inconclusive, since of five who ingested aspirin, three also consumed alcohol. These results emphasize the importance of salicylates in the initiation of ulcer recurrence.

Waterson [*3*] investigated the aspirin habits of 151 patients with gastroduodenal hemorrhage and found that 117 (78 per cent) took aspirin and thirty-four (22 per cent) did not. Twenty-one per cent of the former group complained of gastric intolerance symptoms. Evaluation of these reactions in some of the patients is complicated by the fact that a mixture of codeine and aspirin was taken, the codeine possibly accounting for the intolerance symptoms.

Lange [*5*] in 1957, demonstrated a higher incidence of salicylate ingestion in a group of patients with gastroduodenal bleeding in whom no abnormalities were evident on roentgenograms than in a group of patients with bleeding and roentgenographically demonstrable peptic ulcers (56 per cent in the former compared to 37 per cent in the latter). It is implied that the group with no abnormalities on roentgenograms bled from acute erosive gastritis caused by the ingestion of salicylates. Lange also inferred a greater susceptibility to hemorrhage in the chronic "aspirin addict" than in the casual user, but the differences in incidence were too small to warrant this assumption.

A contrary opinion was held by Alvarez [*6*] who reviewed the records of 103 patients with massive gastrointestinal bleeding. They were divided almost equally into two groups: (1) those who admitted to the ingestion of salicylates prior to hospitalization and (2) those who did not. Twenty patients in the former group and twelve in the latter came to laparotomy. In group 1, seven patients (35 per cent) were found to have acute gastric lesions; in group 2, three patients (25 per cent). Although the authors concluded

that they found no difference in the mucosa of patients who received aspirin preoperatively, these figures do suggest a relationship between aspirin and acute erosive gastritis.

Allibone and Flint [*7*], studying the etiologic factors important in peptic ulcer, held aspirin to be a rare cause of gastroduodenal bleeding. They found the incidence of aspirin consumption to be the same in a group of patients with gastric bleeding and perforation as in a control group. However, it is our opinion that the results may be questioned because of the poor selection of control cases. The control group was comprised of surgical emergencies and accident cases in which there was an unusually high incidence of acute infections of the respiratory tract and asthmatic bronchitis. The aspirin consumption would naturally be high in such patients and would unduly weight this group among them. In fact, re-analysis of their data several months later brought to light the fact that the aspirin consumption in the patients with acute ulcer and hemorrhage was twice that of the control subjects. Consequently, in a later report they admitted the possibility that aspirin could be an important cause of gastrointestinal bleeding. This study re-emphasizes the vital importance of adequate selection of control subjects in collecting data on this problem.

Davis [*28*] also makes the interesting suggestion that in studies in which aspirin consumption is high, the taking of aspirin may have been fortuitous and related to psychosomatic factors which are more prevalent in patients who hemorrhage, prior to the bleeding incident. The ingestion of aspirin is considered by him to be a response to emotional stress and is presumed to have no direct causative relationship to the bleeding.

Muir [*8*] also noted a much higher incidence of recent aspirin ingestion in a group of patients with gastroduodenal hemorrhage than in a group of control subjects (50 per cent as compared to 15 per cent). However, of the total group of 106 patients with gastrointestinal bleeding, in only fourteen (13.2 per cent) could the bleeding be definitely attributed to aspirin.

It is our belief that much of the diversity of opinion and discordant results on the question of aspirin-induced bleeding is explained by variation in the composition of the study and control groups. In many instances, little information is given as to the validity of the diagnosis concerning the source of hemorrhage. Delay in roentgenographic studies and insufficient endoscopic examinations are responsible for overlooking many acute gastric and duodenal ulcers and other bleeding lesions with which the ingestion of aspirin may merely have been a fortuitous coincidence. More fruitful observations might have been made if detailed follow-up studies were performed on patients with bleeding who took aspirin to note their subsequent response to salicylates. The causal associations which are often merely presumptive could then be more firmly established.

There have been several reports in the literature attesting to the ability of aspirin to produce gastrointestinal injury, using aspirin test meals. Muir [*8*] and Schneider [*9*] found gross blood in Levin tube aspirations after aspirin ingestion whereas none of the control group receiving a placebo test meal showed evidence of bleeding in the gastric contents.

Studies of aspirin-induced fecal occult bleeding were performed by Lange [*5*] using the regular, coated, and alkali-combined drug. A significantly higher incidence of positive stools was obtained with each of the aspirin preparations used, confirming its noxious action on the gastrointestinal mucosa. Full acceptance of these conclusions is hindered by several considerations. First, Lange did not exclude an organic gastrointestinal lesion in his test cases as a cause of the occult blood loss. Secondly, in a large number of the patients not given aspirin the stools were also positive because of the extreme sensitivity of the Gregersen's benzidine test employed and the failure to prescribe a meat-free diet. Thirdly, Lange did not state the number of patients in whom the results were positive, merely the number of positive and negative specimens. Fourthly, the number of control stool specimens was small in comparison with the number examined during salicylate administration, making the groups statistically incomparable. Lastly, it is not clear whether these patients, who were under treatment for rheumatic fever and chronic polyarthritis, obtained steroid drugs during this period, providing an additional source of gastric mucosal injury.

In a meticulously planned study to eliminate falsely positive reactions to occult blood tests, Stubbé [*10*] found that 67.9 per cent of a group of rheumatic patients and 75 per cent of a group of healthy volunteer subjects gave positive reactions to benzidine tests of the stool after taking aspirin in tablet or powder form. The reliability of these

TABLE I
PRIMARY DIAGNOSIS

Diagnosis	No. of Patients
Duodenal ulcer (including one patient with both duodenal and gastric ulcer)	8
Hiatus hernia	5
Cirrhosis of the liver	2
Gastric ulcer	2
Gastric polyp	1
Erosive gastritis	1
Abdominal carcinomatosis	1
Gastrointestinal hemorrhage of undetermined etiology	6
Functional gastrointestinal syndromes with negative diagnostic studies	4
Total	30

results was strengthened by reproducing them on repeated occasions and confining the tests to non-dyspeptic subjects. He demonstrated that the mucosal injury produced by aspirin did not correlate with any subjective dyspeptic symptoms, nor was acid secretory stimulation a necessary concomitant. As for the pathogenesis of aspirin-induced bleeding, a disturbance of the blood coagulation mechanism was excluded. Stubbé considered a local irritative action on the gastric mucosa to be the most likely mechanism of aspirin-induced bleeding. The immediate mechanism of this local irritative action is unexplained, but he rejects the hypothesis of bleeding by diapedesis and rhexis of the gastric subepithelial capillaries.

CASE MATERIAL AND METHODS

The thirty subjects chosen for this study were patients who were being evaluated and treated in the gastroenterology clinic of the Out-Patient Department, or on the Medical and Surgical Services of the City Hospital at Elmhurst. Their ages ranged from twenty-nine to eighty-three years, and there were seventeen men and thirteen women. In most instances the gastroscopic examination was part of the planned diagnostic study of the individual patient. No particular selection was otherwise made; consequently, a variety of gastroduodenal diseases are represented. The primary diagnoses are listed in Table I. As noted in Table II, several of the patients had gastrointestinal conditions in addition to the primary one for which admission was required, for example, two with cirrhosis and esophageal varices, two with cholelithiasis, and one with a gastric leiomyomatous polyp. No patient showed diffuse disease of the stomach, such as acute superficial gastritis. In none of the three patients with the diagnosis of gastric ulcer was the ulcer visualized gastroscopically. This was due to the fact that one had already undergone healing and the ulcers of the remaining two patients were located in the gastroscopic "blind areas."

The procedure used in the study was as follows: After an overnight fast, each patient was given a premedicant of 120 mg. sodium phenobarbital two hours prior to gastroscopy and 100 mg. demerol hydrochloride plus 0.4 mg. atropine sulfate a half hour prior to examination. The patients studied in the outpatient department received 25 mg. of Phenergan® as a substitute for Demerol.® The mouth and pharynx were then anesthetized with 1 per cent pontocaine solution. An Ewald tube was gently introduced and the stomach was drained as completely as possible of all secretions. The first (control) gastroscopy before the administration of aspirin was then performed and all deviations from the normal appearance of the mucosa, however minor, were recorded. After withdrawing the gastroscope and placing the patient in the sitting position, three tablets (15 gr.) of aspirin were carefully deposited with a laryngeal forceps at the cricopharyngeus sphincter of the esophageal orifice, and the patient was instructed to swallow. This maneuver circumvented the hazard of tracheal aspiration which could result from pharyngeal anesthesia. In a few patients, in the early part of the study, two tablets (10 gr.) of aspirin were used, but most subjects received three tablets as we found that this number provided us with the best opportunity for visualization of the aspirin and was still within the therapeutic range. After the tablets were swallowed, the patient was again placed in the recumbent position and rotated in an attempt to have the aspirin in contact with as much of the gastric mucosa as possible. The second gastroscopy was performed approximately ten minutes after the aspirin was swallowed. The aspirin, in most instances, was already undergoing rapid dissolution by this time. Careful note was made of the site and nature of all fresh changes in the mucosa including congestion, hyperemia and hemorrhage. Any alteration in the appearance of the folds, collections of mucus, and the presence of erosions were looked for. Observations were made as to the physical state of the aspirin and its relationship to the mucosal changes. The findings were evaluated relative to the initial gastroscopy. In all patients at least two observers checked each other's findings, and in more than half the cases three observers were present to note the changes. As a rule, the observation periods lasted for thirty to forty minutes.

RESULTS

The data collected on each of the thirty patients, including the sex, age, diagnosis, history

of previous gastric distress with aspirin, the appearance of the mucosa before and after aspirin administration, with pertinent comments, are presented in Table II. The aspirin was visualized in all but one case (Case 10). Generally, the aspirin was seen to have disintegrated into a pulverized state and in some instances into small, scattered, discrete fragments, having broken up in the layer of gastric juice remaining in the stomach. Frequently it appeared as a white gelatinous mass of granules adherent to the mucosa in the region of the cardia but in many cases, scattered more distally, in the antrum and around the angulus. The mucosa remained either flat or heaped up in rugose folds about the aspirin.

The control gastroscopic examinations performed before the ingestion of aspirin disclosed a total of twenty-three pathologic changes in sixteen of thirty subjects—thirteen patients with hemorrhagic areas ranging from a minute pinpoint of fresh blood to more extensive areas covering a few centimeters. Some of these areas were considered to be traumatic. There were three patients with scattered petechiae, three with small localized areas of gastritis (two atrophic and one hypertrophic), two with scattered superficial erosions, and two with benign mucosal polyps. The remaining fourteen subjects showed no abnormalities.

The changes induced following the introduction of the aspirin are summarized in Table III from the data in Table II. No change was noted gastroscopically in seventeen patients. In seven patients there was slight congestion of the mucosa surrounding the aspirin. This consisted of a noticeable increase in redness and distinct hyperemia confined to the folds around the aspirin fragment, demarcating this zone from the orange-pink mucosa surrounding it. No break in the mucosa or blood ooze could be detected in these instances, In six patients more intense changes were noted: four showed the aspirin lying in a lake of either fresh or altered blood (hemolyzed by gastric hydrochloric acid), and two showed an increase in bleeding over that which was seen at the time of the control gastroscopy. In some of these six patients the aspirin fragment consisted of an agglutinated gelatinous mass suspended in a lake of blood mixed with fresh mucus. There were no instances of erosion or ulceration after aspirin ingestion in any of the thirty subjects. However, in the patients with bleeding, the mucosa underlying the aspirin was obscured by the blood lake so the possibility of an erosion here could not be excluded.

In Table IV a comparison is made between the control gastroscopic findings in the subjects revealing no reaction to the aspirin, designated as "negative," and in those showing a change after the administration of aspirin, designated as "positive." It will be seen that in eight of thirteen patients (61.5 per cent) designated as "positive" a pathologic condition of the mucosa was evident before aspirin ingestion, as compared with eight of seventeen (47 per cent) designated as "negative." Focusing on the incidence of hemorrhagic change before the administration of aspirin in particular in these two groups, 46 per cent of the "positive" group (six of thirteen) showed this change compared to 35 per cent of the "negative" group (six of seventeen).

As shown in Table IV, fourteen of the thirty subjects exhibited no deviation from normal at the time of the control gastroscopy. Of these fourteen, five (36 per cent) showed congestive or hemorrhagic change after aspirin ingestion. In the group of sixteen patients in whom various types of pathologic changes were evident at the time of the control gastroscopy (before aspirin ingestion), eight patients (50 per cent) revealed additional change consisting of either congestion or hemorrhage after aspirin was administered.

Twenty-eight patients of the entire group gave a history of aspirin ingestion in the past. Four used aspirin very frequently (or habitually), i.e., several times weekly, with multiple doses during the day; seven used aspirin moderately, several doses for one or two days at intervals of weeks or months; and seventeen used aspirin occasionally.

Among the thirteen patients who showed varying degrees of irritation to aspirin gastroscopically, four were moderate users of aspirin and seven took aspirin occasionally; one patient of this group stated that he never took aspirin to his knowledge, and no history was obtained from one. Of the seventeen patients with no change in the gastric mucosa following aspirin ingestion, two used aspirin heavily, four moderately and eleven occasionally.

The "positive" and "negative" reacting groups (to aspirin) were also subdivided as to their experience with gastric intolerance to aspirin. Seven of thirty patients (23.3 per cent) gave a history of intolerance symptoms, two from the "positive" group, and five from the "negative" group, representing 15 per cent and 29 per cent of their respective groups. The

TABLE II

SUMMARY OF DIAGNOSTIC DATA AND GASTROSCOPIC FINDINGS IN THIRTY SUBJECTS BEFORE AND AFTER ADMINISTRATION OF ASPIRIN

Case No.	Sex and Age (yr.)	Diagnosis	Previous Use of Aspirin	Previous Intolerance Symptoms to Aspirin	Control Gastroscopic Findings	Gastroscopic Findings after Aspirin Ingestion	Comments
1	F,70	Hiatus hernia, atrophic gastritis	Occasional	Belching; vague abdominal discomfort; no symptoms after buffered salicylate	Area of atrophic gastritis near cardia on posterior wall; otherwise normal	Mild congestion	
2	M,83	Gastrointestinal hemorrhage, etiology undetermined	Habitual	Occasional epigastric distress and indigestion	Small areas of hemorrhage near cardia; otherwise normal	Unchanged	
3	M,59	Duodenal ulcer	Habitual	Aspirin relieves abdominal pain; no symptoms after aspirin	Occasional areas of moderate congestion seen; 1 cm. area of hemorrhage noted; otherwise normal	Unchanged	
4	M,65	Gastrointestinal hemorrhage, etiology undetermined, cirrhosis of liver	No history obtained		Gastric mucosa pale with occasional areas of minimal hemorrhage	Mild congestion	
5	M,53	Duodenal ulcer; hiatus hernia	Moderate	None	Normal	Hemorrhage	Hemorrhagic lake seen with aspirin tablet in center; underlying mucosa not visualized
6	M,49	Cirrhosis of liver; esophageal varices; cholelithiasis	Occasional	None	Normal	Hemorrhage	Hemorrhagic lake seen with pulverized aspirin in center in proximal portion of body of stomach near greater curvature; underlying mucosa not visualized
7	M,67	Functional gastrointestinal symptoms	Moderate	Epigastric pain with nausea after aspirin	Normal	Unchanged	
8	F,62	Gastric ulcer; cirrhosis of liver, gastric polyp (submucosal leiomyoma)	Occasional	None	Gastric polyp (submucosal leiomyoma); otherwise normal	Hemorrhage	Tablets seen lying in area of fresh hemorrhage; rest of mucosa normal
9	F,71	Functional gastrointestinal symptoms; antral gastritis	Occasional	Epigastric discomfort after ingestion of aspirin; tastes gritty	Small petechial hemorrhage on lesser curvature; otherwise normal	Unchanged	
10	M 73	Abdominal carcinomatosis	Occasional	None	Small patches of atrophic gastritis	Unchanged	
11	F,54	Duodenitis; hiatus hernia	Moderate	None	Normal	Mild congestion	
12	F,54	Hiatus hernia	Moderate	None	Occasional petechiae; minimal mucus	Mild congestion	
13	F,66	Duodenal ulcer	Moderate	None	Normal	Mild congestion	
14	F,47	Gastric ulcer; duodenal ulcer	No previous use of aspirin		Scope could only be passed to depth II; only proximal part of antrum visualized; normal	Mild congestion	
15	F,33	Functional gastrointestinal symptoms	Occasional	Slight nausea	Fresh linear mucosal hemorrhage on lesser curvature proximal to angulus; otherwise normal	Hemorrhage	Instrument passed easily; Ewald tube aspirated altered blood; hemorrhage after aspirin was in area unrelated to control hemorrhage; control hemorrhage was seen unchanged in second examination
16	M,62	Gastric polyp	Occasional	None	Benign gastric polyp seen at angulus; otherwise normal	Unchanged	
17	F,58	Upper gastrointestinal hemorrhage, etiology undetermined	Habitual; no aspirin one week before hemorrhage	None	Normal	Unchanged	
18	M,71	Duodenal ulcer; atrophic gastritis	Occasional	None	Scattered mucosal hemorrhage and areas of congestion; some patchy areas of atrophic gastritis	Mild congestion	Congestion after aspirin seen around granules of aspirin and unrelated to previous changes

TABLE II (*Continued*)

SUMMARY OF DIAGNOSTIC DATA AND GASTROSCOPIC FINDINGS IN THIRTY SUBJECTS BEFORE AND AFTER ADMINISTRATION OF ASPIRIN

Case No.	Sex and Age (yr.)	Diagnosis	Previous Use of Aspirin	Previous Intolerance Symptoms to Aspirin	Control Gastroscopic Findings	Gastroscopic Findings after Aspirin Ingestion	Comments
19	M,29	Upper gastrointestinal hemorrhage, etiology undetermined	Occasional	None	Normal	Unchanged	
20	M,81	Gastrointestinal hemorrhage, etiology undetermined; chronic hypertrophic gastritis	Moderate	None	Normal	Unchanged	
21	M,71	Gastrointestinal hemorrhage, etiology undetermined; rheumatoid arthritis	Moderate	None	Normal	Unchanged	
22	M,54	Cirrhosis of liver, esophageal varices	Occasional	None	Normal	Unchanged	
23	F,49	Functional gastrointestinal symptoms; rheumatic heart disease with chronic heart failure	Occasional; no symptoms from buffered salicylate	None	Normal	Unchanged	
24	M,71	Duodenal ulcer; alcoholism	Habitual use of Anacin®	None	Normal	Unchanged	
25	M,59	Duodenal ulcer; hypertrophic gastritis	Occasional	None	Area of hypertrophic gastritis seen above angulus; otherwise normal	Unchanged	
26	F,39	Duodenal ulcer	Occasional	Abdominal distress after aspirin, similar to ulcer distress	Few areas of fresh hemorrhage seen on mucosa	Unchanged	
27	M,53	Hiatus hernia	Occasional	None	One patch of superficial bleeding from pinpoint hemorrhage near cardia; otherwise normal	Unchanged	
28	F,56	Gastric ulcer	Occasional	None	Two small erosions with small amount of surrounding mucosal hemorrhage	Hemorrhage	More hemorrhage after aspirin with fresh blood in cardia running to area where pulverized aspirin was seen; mucosa surrounding aspirin was normal
29	F,69	Erosive gastritis; cholelithiasis; small hiatus hernia	Occasionally for past six months; heavy previously	None	Many areas of hyperemia; mucosal hemorrhage; few superficial erosions (patches vary in size); scattered on lesser curvature, angulus and anterior wall	Hemorrhage	Response seen in areas previously unaffected with aspirin lying in blood lake
30	M,38	Functional gastrointestinal symptoms	Occasional	None	Normal	Unchanged	

symptoms were more severe in the "negative" group and included epigastric discomfort, gnawing pain, heartburn, nausea, vomiting, bloating and "gas."

None of the thirty patients had previously experienced gastrointestinal bleeding of presumed aspirin origin. Of the six patients who demonstrated the more severe hemorrhagic reaction to aspirin gastroscopically, only one experienced ill effects from the drug taken orally and he described it as mild nausea.

Of the five patients who were discharged with a diagnosis of gastrointestinal hemorrhage, etiology undetermined, none showed any reaction to the aspirin gastroscopically, and only one gave a history of mild epigastric distress with use of the drug.

COMMENTS

The production of local irritative and destructive lesions of the human gastric mucosa by the administration of aspirin has been stressed by many different workers since the initial gastroscopic observations of Douthwaite and Lintott [*11*] in 1938, referred to in the introduction of this report. In the following year, Hurst and

TABLE III
SUMMARY OF GASTROSCOPIC CHANGES IN THIRTY SUBJECTS AFTER TAKING 10 TO 15 GR. OF ASPIRIN

Change	No.	Per cent of Total
None	17	57
Mild congestion	7	23
Hemorrhage	6	20

Lintott [*12*] performed a gastroscopy on a fifty-seven year old patient with suspected salicylate-induced gastrointestinal bleeding after administering two tablets of aspirin. The folds on the lesser curvature aspect around the smaller aspirin fragments were hyperemic. An extravasation of blood was observed surrounding the large aspirin fragments which were embedded in the mucous membrane folds. By introducing into the present gastroscopic investigations a preliminary survey of the mucosa, we avoided the error of attributing all changes observed to the action of aspirin. For example, reference to Table II demonstrates that erosions, varying degrees of scattered congestion, petechiae and hemorrhages were evident in subjects 1 to 4, 8 to 10, 12, 15, 16, 18 and 25 to 29 before the ingestion of aspirin. In several instances the bleeding was obviously fresh and traumatically induced by the introduction of the aspirating Ewald tube, resulting in a tiny lake of coagulated altered blood. The source of the other small petechiae, hemorrhagic lesions and erosions is obscure but they were of the type commonly seen in so-called "normal" gastroscopic examinations. The site and character of these lesions were carefully noted and observed to be distinct from those attributed to the action of aspirin itself. Douthwaite [*11*] preceded his examination of the patient by aspiration with a stomach tube. The extent of congestion or hemorrhage induced thereby remains unaccounted for in his analysis. This accounts for the striking difference in the final results obtained in our studies, namely 43 per cent (Table III) of subjects showing vascular changes after aspirin administration, as compared to 80 per cent reported by Douthwaite. Nevertheless, a 43 per cent incidence is sizeable, and warrants the conclusion that aspirin can act as an exogenous irritant, producing inflammatory changes in the gastric mucosa.

The disparity between the results obtained by our group and those of Paul [*13*] is explained by several factors: (1) Because of his failure to withdraw the gastric contents prior to gastroscopy, the protective layers of mucus remained intact, strengthening the defensive mechanism of the mucous membrane of the stomach. In many of our "positive" cases a recognizable lake of mucus accumulated intimately mixed with the small gelatinous mass of blood, indicating the protective reaction induced. (2) Paul's failure to perform a preliminary control examination hampers interpretation. For example, seventy-five of the 182 patients in Paul's group I and nineteen of his twenty-seven patients with gastric ulcer exhibited a variety of pathologic changes, including "chronic gastritis," pigment spots and ulcers when aspirin was administered initially, none of which he attributed to the drug. No clear definition is provided by Paul as to the mucosal alterations included under the term "chronic gastritis." Recent mucosal biopsy studies indicate the lack of specificity of this

TABLE IV
COMPARISON OF CONTROL GASTROSCOPIC FINDINGS BETWEEN PATIENTS WITH A "NEGATIVE" AND "POSITIVE" REACTION TO ASPIRIN

Negative Reaction	No. of Patients	Positive Reaction	No. of Patients
Normal	9	Normal	5
Varying degrees of hemorrhage	5	Varying degrees of hemorrhage	3
Chronic patchy gastritis	2	Chronic patchy gastritis (including hemorrhage in one)	2
Polyp (also showed hemorrhage and petechiae)	1	Polyp	1
		Gastric erosions (both including hemorrhage)	2
Total	17	Total	13

diagnosis and demonstrate that certain changes, such as edema, congestion, hemorrhage and mucus secretion, are common to both the acute and chronic phases. In view of these facts, a proportion of the pathologic alterations seen in the initial examination may well have been due to irritation induced by contact with aspirin.

Caravati's gastroscopic study [*15*] also lacks preliminary control data. It is not surprising that a reaction was not obtained by him when salicylates were administered intravenously, as our work would seem to indicate that the drug has a local irritant action on direct contact. With respect to his eight subjects who received daily doses of sodium salicylate orally, there is no indication as to the time interval between the final dose and the gastroscopic examination. Minor degrees of hyperemia and congestion could disappear within several hours.

The failure of Wolf and Wolff [*17*] to elicit an inflammatory change with aspirin in their patient with fistulas may have been due to the resistant nature of the gastric mucosa after forty-seven years of fistulization. Furthermore, only a small portion of the entire gastric mucosa was visible in their experiment.

Our investigation demonstrates an even greater incidence of the more severe degrees of vascular change than that reported by Douthwaite (20 per cent as compared with 13 per cent). Hurst and Lintott [*12*], Douthwaite [*16*], and Muir [*8*], stressed the fact that the site of most intense action in the stomach was the lesser curvature aspect. However, our own studies indicate no greater susceptibility of this area over any other region. In some instances the area of congestion or hemorrhage produced by aspirin was located near the cardia; in others the posterior wall of pars media or even the anterior wall was most affected. By rotating many of our subjects through almost 360 degrees, we obtained a greater dispersion of the aspirin fragments on the gastric wall, demonstrating its ability to irritate all areas of the gastric mucosa. Unfortunately, no positive statement can be made from our studies regarding the erosive or ulcerogenic action of aspirin because, in the more marked cases of bleeding, the pulverized mass of aspirin, coagulated blood, and mucus formed an adherent gelatinous layer of 10 to 15 mm. in diameter, obscuring the underlying mucosa from view. A destructive action was emphasized by Muir and Cossar [*18*] who demonstrated gastric erosions and ulceration in excised stomach specimens from patients with duodenal ulcer given aspirin two hours prior to gastrectomy. It is our belief that the conditions under which this experiment was performed provided the setting and basis for ulcerative changes on entirely different mechanisms. The stress of scheduled surgery causing increased psychogenic vagal tone and steroid output, anesthesia and traumatic shock during surgery, change in acid-pepsin and mucus output, blood loss and clamping of blood vessels may have contributed more to the production of erosive change than the action of the aspirin. The mucosa was not seen in its natural state, and no observations were recorded of the appearance of the gastric mucosa prior to surgery and aspirin administration.

An interesting point deduced from our findings is the greater susceptibility of the patient with peptic ulcer to gastric irritation by aspirin. The tabulated data indicate that six (Cases 5, 8, 13, 14, 18 and 28) of the ten patients with peptic ulcer, 60 per cent showed hemorrhage or congestion, whereas only seven of the twenty patients without ulcer (35 per cent) showed these changes. Almost half of the total "positive" group were patients with peptic ulcer; the tendency to bleed after the ingestion of aspirin was twice as great in the patient with peptic ulcer disease. Consequently, increased caution is warranted in prescribing salicylates for such persons—a warning sounded by previous investigators (Hurst [*14*], Brown and Mitchell [*4*], Schneider [*9*], Muir and Cossar [*18*]).

Reference to our findings (Table IV) brings to light the fact that the person who has some pathologic condition of the gastric mucosa to begin with may be slightly more susceptible to injury with aspirin than the person with normal mucosa. This is shown by the higher incidence of inflammatory change after aspirin intake among the patients showing some pathologic condition at the time of the control gastroscopy (58 per cent as compared to 36 per cent). Also, more of the patients who demonstrated a hemorrhagic reaction to aspirin had pathologic changes prior to aspirin ingestion.

A lack of correlation between the occurrence of subjective gastric distress and the incidence of aspirin-induced bleeding was shown by the infrequent history of gastrointestinal symptoms obtained in the subjects who showed hyperemia and bleeding gastroscopically (15 per cent as compared to 29 per cent of those subjects who exhibited no change after aspirin ingestion).

None gave a history of presumed aspirin-induced bleeding in the past.

Since only the uncoated, unbuffered, whole aspirin tablet was employed in this investigation, no information is available as to any claimed superiority of other forms of the drug. Thompson and Dragstedt [*30*] concluded that any advantage held by calcium aspirin, by reason of its greater solubility, is outweighed by its ready hydrolysis by atmospheric moisture, leaving the acetylsalicylic acid free to exert its action.

After reviewing the evidence, Cronk [*31*], Levy and Hayes [*32*], and Rubin, Pelikan and Kensler [*33*] admit the gastric irritative effects of aspirin, but assert that they are largely a function of its rate of dispersion, disintegration and dissolution within the gastric lumen. A number of our "positive" patients showed congestive and bleeding changes around very small or completely disintegrated particles of aspirin, and it was our impression that the degree of pulverization had little influence on the extent or severity of change. Contrariwise, whole, unbroken and unpulverized tablets were seen gastroscopically in a few of the "negative" patients without any mucosal alteration.

No completely acceptable explanation is forthcoming, as yet, regarding the precise mode of production of aspirin-induced gastric bleeding. The bishydroxycoumarin-like action of salicylates suggested by Meyer and Howard [*34*], Shapiro, Redish and Campbell [*35*], and Smith [*36*] has not been verified by Hurst and Lintott [*12*], Kelly [*19*], Modell and Patterson [*27*], and others, all of whom found no disturbance of the prothrombin mechanism of the blood in their cases of aspirin-induced gastric bleeding.

Warthin [*37*] believes the effects produced by aspirin on the stomach are a manifestation of an allergic response. According to this concept, the subjective gastric distress as well as the bleeding produced by aspirin are explained on the basis of varying degrees of hypersensitivity or differences in susceptibility to the drug displayed by the individual tissues, namely, the muscle, glands or capillaries of the gastric wall. Although allergic exudative responses in the stomach have been demonstrated gastroscopically (Paviat and Chevallier [*38*], and Pollard and Stuart [*39*]), the chemical agent inciting the local hyperimmune state was always a heterologous protein. Among other changes, a diffuse exudation of fluid in the form of edema and profuse mucus secretion were prominent features of the pathologic alterations. It is highly improbable that this is the fundamental mechanism of aspirin gastric irritation. Furthermore, none of our "positive" patients gave a personal or family history of other allergic manifestations. Also, we observed no noticeable edematous change in the gastric mucosa from the addition of aspirin. Lastly, when mucus secretion did occur, it formed a small localized collection in the vicinity of the aspirin fragment rather than a diffuse generalized response of the entire gastric mucosa.

Another attractive hypothesis, with supporting experimental evidence, is the adrenocorticotropic effect of salicylates shown by the work of Cronheim, King and Hyder [*40*]. Although acetylsalicylic acid was not tested, a variety of substituted salicylic acid compounds were investigated and practically all showed this effect. This work suggested that aspirin might affect gastric mucosa through the pituitary adrenal mechanism in the manner of stress ulceration. It is hardly likely, however, that the rapid mucosal changes noted in our gastroscopic studies, with aspirin still lying in the gastric lumen, could act through the medium of any general steroid response.

An alteration or decrease in the secretion of gastric mucin, causing interference with the defensive mechanism of the stomach mucosa, has also been suggested as the underlying disturbance caused by aspirin [*19*]. This theory however, is not supported by the experimental evidence, which demonstrates an augmentation rather than a diminution in the mucoid-diluting secretion of the stomach with aspirin solutions [*2*].

Finally, in view of the nature of the discrete mucosal hemorrhages and areas of congestion observed gastroscopically at the sites of contact with aspirin, it is our impression that the noxious action is a local one and consists of direct vascular injury, involving the capillaries in the lamina propria layer of the mucous membrane. Hemorrhage from this capillary plexus, which lies directly beneath the surface epithelial layer in the connective tissue of the lamina propria, could lead to hypoxia and subsequent necrobiosis of the neck stratum of the gastric gland tubule. Exfoliation of the foveola of the gland tubule would then result in the formation of an erosion. This sequence of changes could explain the mucosal hemorrhages seen by us and the erosive changes described by other workers. Hemorrhagic and erosive gastritis have, in fact,

been demonstrated to result from a variety of noxious agents exerting a deleterious action on the intricate capillary plexus in the lamina propria of the stomach. This inherent susceptibility is due to the unusual arteriovenous shunt mechanism in this layer [*41*]. In this connection, the recently improved gastroscope, with its attached suction biopsy device, which enables the operator to obtain a specimen from any visualized area of the gastroscopic field, might be useful in throwing additional light on the precise histologic changes occurring at the site of aspirin injury.

SUMMARY AND CONCLUSIONS

A study of the effects of aspirin on the gastric mucosa observed gastroscopically in thirty subjects is presented, with a review of the pertinent literature.

Forty-three per cent of the subjects studied reacted to the administration of aspirin with congestive and hemorrhagic changes of the gastric mucosa. These effects occurred predominantly around areas in contact with and in close proximity to the drug. Evidence is presented that objective evaluation of the local effects of a drug by gastroscopy requires comparison with preliminary control observations of the gastric mucosa.

Patients with peptic ulcer were slightly more susceptible to mucosal injury with aspirin, as were those subjects with pre-existing minor mucosal changes such as minimal hemorrhage or patchy gastritis, as seen in the control observation.

There was no correlation between symptoms of intolerance to aspirin and the occurrence of hemorrhagic phenomena.

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Review

Chronic Pulmonary Emphysema*

Anatomy and Pathogenesis

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Pulmonary emphysema with or without chronic bronchitis is commonly regarded as a major cause of disability and of death, but the nature of the disease processes covered by the term emphysema is still poorly understood. Despite the increasing attention devoted to emphysema by clinicians, roentgenologists, physiologists and pathologists, its definition lacks clarity because each group of investigators inevitably tends to emphasise its own criteria but is unable to give sufficient attention to the characteristic features observed or derived by other disciplines. Physiologic technics analyse lung function in terms of its basic elements—ventilation, diffusion and perfusion—but the results usually refer to lung function as a whole and do not distinguish particular nosologic entities. Gilson and Hugh-Jones [*1*], for instance, stated that it is logical to define emphysema in terms of lung function, but admitted that in so doing they included under the term emphysema a variety of conditions showing similar functional changes but caused by different disease processes producing differing signs and symptoms. Fishman [*2*] expressed a similar view. It is thus reasonable to conclude that physiologic criteria do not yet provide a sufficient basis for the definition of emphysema. We believe that at present morbid anatomy affords a more fundamental approach to the problem and this belief is reflected in current clinical opinion [*3*]. It is no longer sufficient to dismiss the pathologic features of emphysema by saying that in this condition the lungs are voluminous and inelastic, that their parenchyma is destroyed and the capillary bed diminished [*4,5*], since different structural forms of emphysema can now be distinguished from each other and from related conditions.

PRELIMINARY CONSIDERATIONS

The anatomy of emphysema may be studied in two ways, the choice being influenced by the source of the material. One, and at first sight the more attractive approach, is to study lungs from subjects who were thoroughly investigated clinically and physiologically and who died from emphysema in order to establish a clinicopathologic correlation. The value of such material is limited by the fact that, in dealing with a pathologic end-state, different disease processes may well be rendered indistinguishable by extensive destructive changes. Lungs in this state are not uncommon and can only be described by a non-specific term such as chronic pulmonary destruction. A close parallel is provided by chronic renal destruction, which is recognised to be the end result of several conditions, initially quite distinct not only in regard to structural changes but also in regard to aetiology. The second approach attempts to determine the initial lesions in the various processes included under the term emphysema, that is before non-specific destructive and inflammatory changes ensue. This method involves the study of material from subjects who were not investigated physiologically and who probably died from non-pulmonary conditions, as well as from subjects with clinical emphysema.

The gross appearance of the emphysematous lung may well indicate the extent and severity of the disease, but it does not give a sufficiently precise idea of the anatomic nature of the lesion

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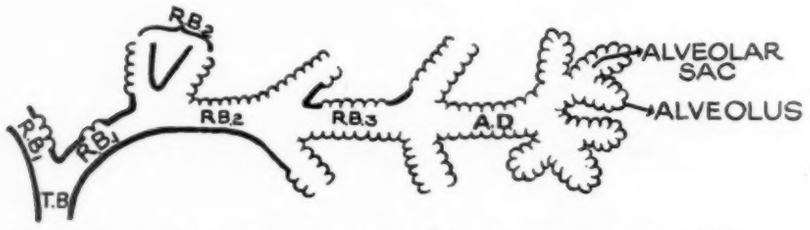


FIG. 1. Diagram of the normal anatomy of the respiratory portion of the bronchiolar tree. T.B. = terminal bronchiole. R.B.1, 2 and 3 = orders of respiratory bronchiole. A.D. = alveolar duct.

and thus forms an inadequate basis for definition. Moreover, the classification of emphysema on its macroscopic appearances has led to the introduction of confusing terms, such as diffuse generalised, focal generalised and localised diffuse emphysema. We therefore propose to define emphysema in terms of microanatomy. The ultimate basis for the definition and classification of disease must be aetiologic and the present reliance on pathologic anatomy is but a step towards this objective. Microanatomic investigations, especially in early cases, have in fact suggested pathogenetic possibilities.

Microanatomic studies of the lung necessitate a standardised technic for the preparation of specimens. Ideally every lung should be preserved in a state which corresponds to its natural size at a given point in the respiratory cycle. The size of lungs fixed *in situ*, whether by intratracheal or intravascular injection, is affected to an unpredictable degree by the posture of the body as well as by postmortem abdominal distention [*6*]. Measurements made on excised lungs distended by intrabronchial injection of fixative, whether at constant pressure or not, are open to the criticism that in lungs of high compliance (e.g., emphysema) air spaces will distend to a proportionately greater degree than in specimens of normal or low compliance. Since there seems to be no known way of avoiding this difficulty we have fixed excised lungs simply by intrabronchial infusion of neutral formol-acetate solution under low pressure until the pleura is rendered uniformly smooth and in some instances the main bronchus and vessels have been clamped to minimise shrinkage. Random histologic preparations give an imperfect idea of lung structure and hence in our investigations large blocks of lung tissue were sectioned in strict series so as to obtain a three-dimensional concept.

To understand the microanatomic changes in emphysema, it is necessary to delineate the normal structure of the lung, especially the respiratory portion. The number of orders of nonrespiratory bronchioles is variously given as between 5 and 10 but, along with von Hayek [*7*], we accept the lower figure, although the number is not always constant in different parts of the same lung. The most distal order of nonrespiratory bronchiole is customarily designated the terminal bronchiole. From this there usually proceed three successive orders of respiratory bronchiole, i.e., bronchioles bearing alveoli in increasing numbers as the airway is followed distally. After the respiratory bronchioles comes the single order of alveolar duct which is completely lined by alveoli and leads in turn to the alveolar sacs with their alveoli [*8*]. (Fig. 1.) The territory supplied by a terminal bronchiole may be described as an acinus [*9*].

PRIMARY DEFINITION

The word emphysema denotes inflation and, in regard to the lung, Laennec [*10*] probably made the earliest attempt at an anatomic definition. He distinguished two varieties of emphysema, interlobular and vesicular. Interlobular emphysema is now described as interstitial and with this form we are not concerned. Vesicular emphysema, according to Laennec, could be regarded as an exaggeration of the natural condition of the lung, the size of the vesicles being much increased, although not always uniformly. Large vesicles were probably produced by fusion of several air cells through destruction of the intervening partitions, but sometimes they appeared to arise by simple dilatation of a single vesicle. No better basis for an anatomic definition has been propounded but it is impossible to say whether Laennec's "vesicle" can be equated with any particular segment of the airway as it is now known. It seems safe to conclude, however, that since this "vesicle" was visible to the naked eye it is most unlikely to correspond with the modern alveolus.

The complexity of the pulmonary architecture has only been exposed since Laennec's time and in order to give recognition to modern knowledge of lung structure the term emphysema now needs to be made more explicit. This necessity became apparent when the microanatomy of focal emphysema was first established, and it was then concluded that the enlarged air spaces of emphysema could be taken to originate from any segment or group of segments of the bronchiolar tree in which haemorespiratory gaseous exchange is or was possible [*8*]. In other words chronic emphysema is to be regarded as a persistent enlargement of respiratory bronchioles, alveolar ducts or alveolar sacs as well as of their associated alveoli, and this basis for definition was agreed upon at the Ciba Symposium.

CLASSIFICATION

Laennec clearly recognised the participation of two processes in the production of emphysema, and the relationship of dilatation and destruction must be considered. The identification of a destructive element is relatively easy when there is a breach of continuity in the walls of respiratory air passages or alveoli, and presumably it is to such manifestations that the term destructive is generally applied. However, persistent enlargement of respiratory air spaces from whatever cause probably leads in the course of time to atrophy of the tissues comprising the walls of affected spaces. Atrophy may justifiably be regarded as a degree of destruction, even though it has not proceeded far enough to cause actual breach of interalveolar partitions. The possibility of this double use of the term destruction has been overlooked and it thus loses much of its value as a basis of distinction between types of emphysema. Moreover, gross destruction of pulmonary elements is frequently a non-specific secondary manifestation in forms of emphysema which, in their earlier stages at least, can be differentiated on other grounds. To indicate those cases in which the walls of alveoli or respiratory bronchioles show a distinct breach of continuity we propose to adopt the purely descriptive term of disruptive emphysema without implications as to causation.

By three-dimensional studies we have found that in certain varieties of emphysema the enlargement may affect particular segments or a combination of segments of the bronchiolar tree and also that in some forms the enlargement is associated with other changes of a characteristic nature. From the morphologic standpoint, therefore, we prefer to classify chronic pulmonary emphysema on the basis of the distribution of the enlargement (Table I) and at the same time to indicate when disruptive emphysema exists.

TABLE I

CLASSIFICATION OF CHRONIC PULMONARY EMPHYSEMA ACCORDING TO THE AIRWAYS MAINLY AFFECTED

(1)	Respiratory bronchioles
	(a) Focal emphysema due to dust
	(b) Centrilobular emphysema
(2)	Alveolar ducts and alveolar sacs
	"Vesicular" emphysema
(3)	Irregular
	Scar emphysema

NOTE: See text regarding "panacinar" emphysema.

The word "vesicular" has already been used to describe the second category [*8*], but it may be objected that according to Laennec "vesicular" refers collectively to all forms of non-interstitial emphysema. To avoid confusion the adjective "vesicular" will be placed in quotation marks when it is used to describe the second category of emphysema.

Respiratory bronchioles are characteristically affected in two distinct types of emphysema, to distinguish which the terms focal emphysema and centrilobular emphysema have been adopted.

FOCAL EMPHYSEMA

Focal emphysema occurs in persons exposed to an industrial dust hazard and forms one of the main features of simple pneumoconiosis due to dusts with a low or negligible content of free silica. Although it is usually connected with coal workers, focal emphysema is not restricted to these men but occurs for instance in haematite, graphite and foundry workers and also after the inhalation of purified carbon. A mild degree of focal emphysema may occasionally occur in the pigmented lungs of town dwellers who had no history of occupational exposure to dust.

Simple pneumoconiosis, as seen for instance in coal workers, is characterised by numerous, discrete foci of dust widely scattered throughout the lung. These foci are sometimes larger and more numerous in the upper parts of the lung and there may be 2 to 5 lesions on the cut surface of a (secondary) lobule, i.e., that part of the lung more or less demarcated by fibrous sep-

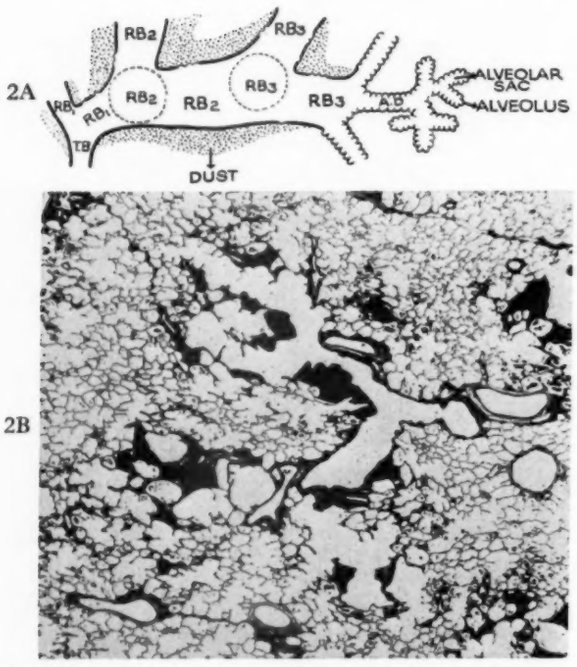


FIG. 2. The microanatomy of focal emphysema as seen, for instance, in coal workers. A, diagrammatic representation, symbols as in Figure 1. B, actual lesion, showing focal emphysema, mostly in longitudinal section. Original magnification × 10.

tums. The dust foci possess three principal features: a large amount of dust, a relatively small amount of fibrous tissue, and frequently enlarged air spaces in and around the dust. When studied by means of serial sections it is found that the dust accumulates preferentially around the three orders of respiratory bronchioles and, furthermore, it is these same bronchioles which dilate to form the enlarged air spaces of focal emphysema [*8*]. (Fig. 2.) It should be emphasised that bronchiolar stenosis does not occur, that bronchiolitis is not a necessary accompaniment and that initially disruption is not a feature of the focal variety. As the latter condition advances, however, surrounding lung parenchyma is distorted and when severe the lesions apparently become confluent through the supervention of disruptive emphysema. The appearance of the simple dust lesion differs according to whether it is sectioned longitudinally, obliquely or transversely, but these differences can readily be reconciled as manifestations of the same fundamental lesion by means of cinephotography of serial sections [*11*].

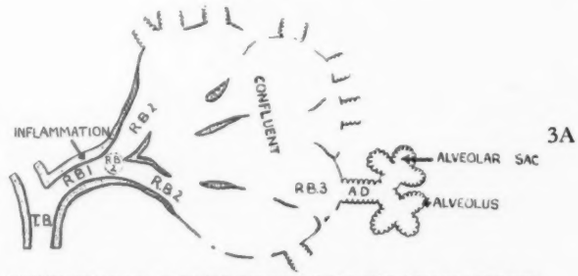
The genesis of focal emphysema, like that of other forms, may be interpreted on a mechanical basis [*12*]. The vesicular tissue immediately around the respiratory bronchioles is consolidated by the accumulation of dust laden phagocytes with little fibrous tissue and cannot therefore fill on inspiration. Nevertheless, the inspiratory traction normally expended on the consolidated alveoli is transmitted to the respiratory bronchioles and adds somewhat to the traction exerted on them. When dust accumulation has led to the development of focal emphysema it is usual to find that the bronchiolar smooth muscle is atrophic or absent. We have not found such severe atrophy or absence of smooth muscle confined to respiratory bronchioles without dust accumulation in non-miners of similar age and have not seen advanced focal emphysema occurring in relation to dust lesions containing a large amount of smooth muscle. In the course of time, expiratory contraction and shortening of the respiratory bronchioles is evidently diminished or abolished by the collection of dust. The combined effect of such interferences with the inspiratory and expiratory movements of the bronchioles is to produce permanent dilatation, that is focal emphysema. In this process, interference with expiratory movement probably plays the major role.

CENTRILOBULAR EMPHYSEMA

In this variety, groups of enlarged air spaces occur towards the centres of lung lobules, the peripheral tissue being uninvolved, at least initially [*13*]. The lung as a whole is often enlarged. The lesion consists essentially of groups of disrupted respiratory bronchioles, in particular those of the more distal orders. (Fig. 3.) Because their walls have been largely destroyed, more than one respiratory bronchiole enters into the formation of an emphysematous space, the outline of which is in consequence irregular. Disruptive emphysema with fusion of spaces probably explains why there are often fewer lesions of centrilobular type than of focal type in lobules of comparable size. Centrilobular emphysema is not necessarily associated with dust collection, occurring both in miners and in the non-industrial population, including women. It is, however, invariably associated with chronic inflammation affecting (1) the non-respiratory or respiratory bronchiole which connects with the emphysematous area (i.e., the parent bronchiole) and (2) the fragmented tissues within the emphysematous spaces, to a lesser and variable degree. Some parent bronchioles are narrowed,

although severe obstruction is uncommon, but in many lesions the parent bronchiole is of normal size or is even wider than normal. Alveolar ducts arising from the periphery of the emphysematous spaces may be of normal calibre, although the changes of "vesicular" emphysema (*vide infra*) may be superimposed. The lesion described by Spain and Kaufman [*14*] apparently represents centrilobular emphysema with a narrowed parent bronchiole.

In the smallest lesions and thus presumably at an early stage of development, centrilobular emphysema clearly exhibits both disruption and a relationship with chronic bronchiolitis. Normally, proximal respiratory bronchioles differ from distal ones in having a greater extent of their walls continuously epithelialised, in possessing more connective tissue elements (including muscle), and in bearing much fewer alveoli. It is therefore understandable that the changes following inflammation could differ at the extremities of the respiratory bronchiolar tree, so that disruption predominates distally whilst proliferation is more evident proximally. The pathologic features suggest that the primary change is a respiratory bronchiolitis, possibly recurrent, with involvement of immediately adjacent alveoli. The evidence does not allow us to say whether the inflammatory process is chronic from the beginning, follows one or more acute episodes, or if the emphysema arises by a rapid or a slow process. Chronic inflammation of the parent (i.e., proximal) bronchioles may well convert them into functionally rigid structures, which are unable to dilate or elongate under the force of inspiration, and it is possible that, in consequence, damage to more distal respiratory bronchioles is aggravated by overstretching.



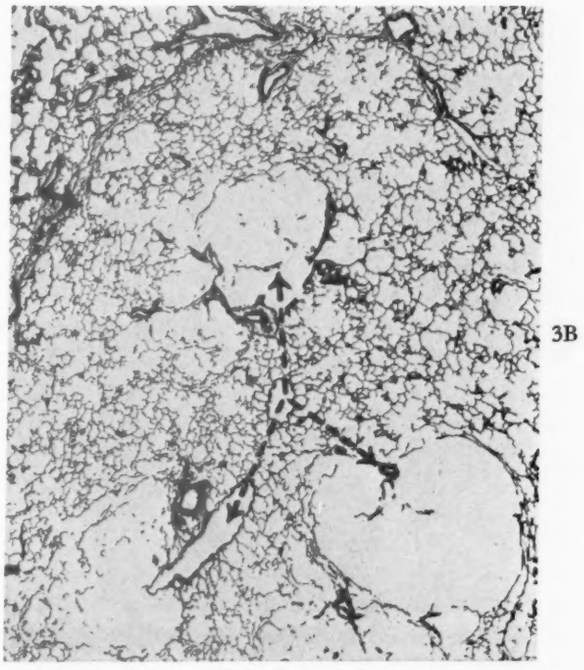


FIG. 3. The microanatomy of centrilobular emphysema. A, diagrammatic representation, symbols as in Figure 1. B, three actual lesions. Broken arrows indicate the course of the parent bronchioles, which arose from a common stem. Short continuous arrow indicates an alveolar duct in free communication with an emphysematous space. A lobular septum occurs in the upper part of the illustration. Original magnification × 10.

"VESICULAR" EMPHYSEMA

This variety may be generalised or localised. When generalised there is a widespread, although not necessarily uniform, enlargement of air spaces, rendering them easily visible to the naked eye. Isolated histologic sections give the impression of intercommunicating spaces of irregular outline. Thinning and rupture of alveolar walls are often held to account for these appearances. That this interpretation is erroneous will be evident when the normal structure of the respiratory airways is recalled. The free extremities of alveolar walls, as seen in histologic preparations, do not represent broken ends but are sections across the rims of the cup-shaped alveoli opening into the respiratory bronchioles, alveolar ducts and sacs. The basic anatomic pattern of the vesicular tissue is not altered initially in this type of emphysema. If, in cases of generalised (i.e., widespread) "vesicular" emphysema, the air passages are traced distally from the terminal bronchiole, the respiratory bronchioles are customarily of normal size, although the third order may be somewhat enlarged. Characteristically it is the alveolar ducts and alveolar sacs which show an increase in diameter and this increase occurs largely at the expense of the associated alveoli which as a result become wider at their mouths and shallower in depth.

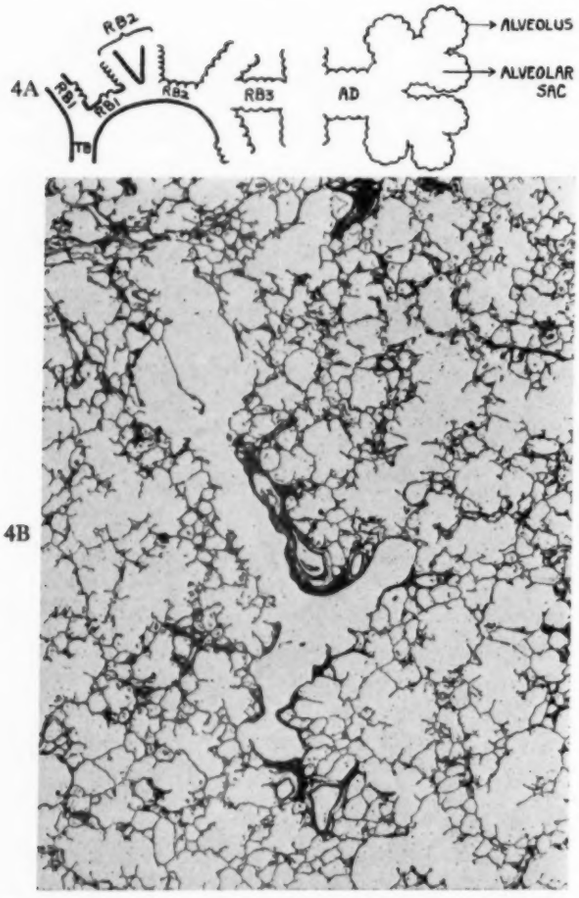


FIG. 4. The microanatomy of "vesicular" emphysema. A, diagrammatic representation, symbols as in Figure 1. B, lung showing the features in longitudinal section. Enlargement of alveoli, alveolar sacs and ducts. First and second order respiratory bronchioles normal in size, but third order somewhat enlarged. Original magnification × 10.

(Fig. 4.) In sections the side walls of the alveoli thus appear shortened. Our findings [*8*] in this connection agree with the observations of Hartroft [*15*]. Whilst the degree of enlargement may vary not only between different cases but also in different parts of the same lung and even between lobules, the over-all appearance is more uniform than in other varieties of emphysema.

After formalin fixation normal lungs shrink in volume to a greater degree than emphysematous ones and hence we had to establish that the enlargement of air spaces in generalised "vesicular" emphysema was genuine and not an artefact caused by the fixation of tissues of different consistencies. The maximum size of air spaces in normal lungs from elderly subjects was determined by intrabronchial distention of warmed specimens to their maximum with warm gelatin, the main bronchi then being clamped. There was no noticeable shrinkage on cooling and the size of the air spaces was determined in frozen sections prepared from different parts of each lung, which it must be stressed was unfixed and had been maintained in a state of distention by the solid gelatin. Alveolar ducts and alveolar sacs were found to be smaller and the alveoli deeper than the corresponding spaces in cases of generalised "vesicular" emphysema in which the lungs had been fixed by intrabronchial infusion of formalin without clamping the bronchi and in which some shrinkage had occurred. We therefore conclude that this form of emphysema exists as a genuine entity.

Pathologically it is customary to distinguish hypertrophic and atrophic or senile forms of generalised "vesicular" emphysema. In the hypertrophic form, already described, the lung as a whole tends to be enlarged but the lungs of elderly people are not necessarily small ones, as Richards [*16*] also noted. The lung architecture of very old people may show little if any deviation from normal as judged by conventional means and in some such instances the preservation of smooth muscle and of so-called elastic tissue is remarkably good. Lungs from other elderly persons show mild enlargement of respiratory airways, especially alveolar ducts and sacs, with some thinning of alveolar walls and lack of cellular and fibrous elements. The anatomic changes in the airways are thus essentially similar in both varieties although they are much less severe in the so-called senile emphysema. The latter is frequently associated with wasting from any cause, but it is not known whether characteristic age changes occur in the lung and, if so, whether they are related to the development of "vesicular" emphysema. Under these circumstances it is perhaps better to avoid the term senile emphysema.

It is exceptional to find chronic inflammatory changes in the respiratory or the non-respiratory bronchioles of subjects with generalised "vesicular" emphysema, and causes for the disease other than chronic bronchiolitis must therefore be sought. Organic obstruction of air passages is not a constant or even a common feature of generalised "vesicular" emphysema. It is widely agreed that in clinical emphysema the chest is maintained in a state of partial inspiration [*17*] with which the anatomic changes of generalised "vesicular" emphysema correspond. To explain

this condition a deficiency of elastic tissue has often been considered but there are reasons for doubting the importance of elastic tissue in expiratory recoil of the lung [*12*]. No theory, however, takes adequate account of the possibility of natural variations in the amount of smooth muscle in the bronchial tree. The expiratory phase of respiration is to a considerable extent due to smooth muscle activity. If the bronchial and bronchiolar muscle is deficient in amount, either naturally or from general wasting, then a state of imbalance could exist in which inspiratory traction is relatively unopposed and, over a prolonged period, might lead to fixation of the thorax in a position of partial inspiration. This view is supported by the fact that chronic asthma, in which bronchiolar smooth muscle is hypertrophic, is rarely associated with chronic generalised "vesicular" emphysema at autopsy [*18*]. It is possible that the thoracic cage may become fixed in the inspiratory position because of skeletal changes [*19,20*] and it could therefore be argued that enlargement of the lungs with atrophy of muscle in the air passages was a consequence rather than a cause of alteration in position of the thoracic cage. Pierce and Ebert [*21*], however, emphasised that barrel deformity of the chest, commonly regarded as an indication of emphysema, may occur independently of any change in the lungs.

As already indicated, the distal order of respiratory bronchiole may be enlarged along with alveolar ducts and sacs in "vesicular" emphysema, but there seems no reason why respiratory bronchioles should not become more extensively involved. It must be remembered that relatively early cases were selected for examination and, had we studied more advanced ones, it is possible that they would have shown dilatation extending more proximally along respiratory bronchioles. If it is established that a form of emphysema may affect all orders of respiratory bronchioles as well as alveolar ducts and sacs, a fourth category will be needed in Table I and for this the term "panacinar" [*9*] could be used. It would then be necessary to decide whether "panacinar" emphysema affects all respiratory segments of the bronchiolar tree from the start or whether respiratory bronchioles are involved after alveolar ducts and sacs. It is reasonable to suppose that a uniform pattern of emphysema could develop in otherwise healthy lung, adjacent to extensive areas of collapse or

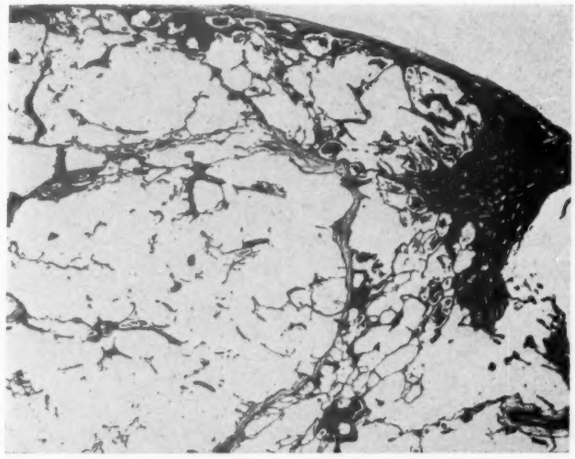


FIG. 5. Irregular emphysema associated with scarring. Gross disruption of lung tissue. Original magnification × 10.

fibrosis, or after lobectomy or pneumonectomy. Uniform enlargement of all respiratory segments occurs in infantile lobar emphysema. The separate recognition of generalised "vesicular" emphysema, as here described, depends on the observation that respiratory bronchioles are inconstantly enlarged and then to a lesser degree than alveolar ducts and sacs. Alveolar sacs, being devoid of smooth muscle, might be expected to suffer from imbalance of the forces of inspiration and expiration before alveolar ducts, which possess muscle. Normally the amount of muscle tends to increase as the respiratory air passages are traced proximally and this may explain why second and first order respiratory bronchioles may escape emphysematous change, at least initially.

IRREGULAR EMPHYSEMA

For those forms of emphysema in which respiratory bronchioles, alveolar ducts or alveolar sacs are affected haphazardly a separate category must be provided. This irregular emphysema is commonly associated with pulmonary scars (Fig. 5), involving bronchioles and parenchyma. A scar may be associated on one side with emphysematous respiratory bronchioles belonging to a particular acinus but on another aspect with enlarged alveolar ducts belonging to a different acinus. However they originate, scars not only contract but also prevent expansion of the affected lung, so that enlargement of surrounding air spaces may result both from primary disruption and from inspiratory overstretching of neighbouring lung tissue. Such air spaces are customarily called emphysematous

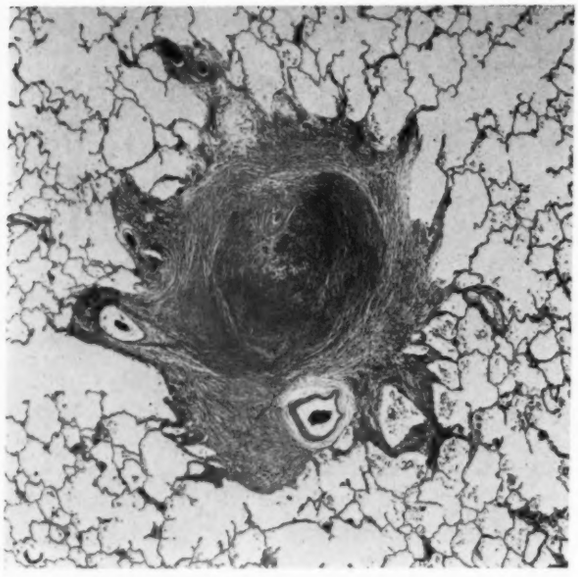


FIG. 6. Silicotic nodule without emphysematous changes in the surrounding lung tissue. Original magnification × 25.

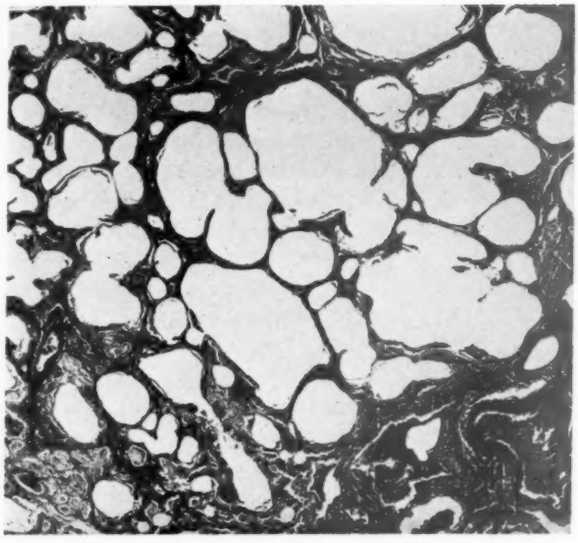


FIG. 7. Honeycomb lung of non-specific type. Original magnification × 10.

and, if this designation is accepted, the general definition of emphysema must include spaces that are partially surrounded by fibrous tissue as well as those which are entirely delineated by alveolar tissue. It is perhaps worth mentioning that pulmonary fibrosis, when diffuse and interstitial in type, is not characteristically associated with emphysema and the affected lungs are usually smaller than normal.

Silicotic nodules may be regarded as falling into the category of pulmonary scars, although possessing special features. The classic silicotic nodule, although it develops at the same site as the coal dust lesion, is not associated with focal emphysema as herein defined. (Fig. 6.) During its period of development, which may continue for years after dust inhalation has ceased [*22,23*], the silicotic nodule is a progressively expanding fibrotic lesion which surrounds and indents respiratory bronchioles. When growth of the nodule ultimately ceases it can then act as a scar, and the surrounding air spaces, whatever their origin, will be somewhat enlarged in consequence. It is important to distinguish the irregular emphysema associated with silicotic nodules from focal emphysema due to dusts containing little free silica.

Irregular emphysema is sometimes disposed along a restricted zone immediately adjacent to septums, bronchi and arteries as well as just beneath the pleura, whilst the remaining lung tissue shows little abnormality. This linear distribution seems to deserve separate recognition [*24*]. It is usually disruptive in nature and slight fibrosis may be associated. Some of the subpleural, paraseptal and parabronchial spaces may even be enclosed by thin fibrous walls and then the condition really falls within the definition of a cystic state (*vide infra*). The existence, at least in some instances, of a fibrous element suggests that the initial change may be inflammatory in nature. It is, however, difficult to account for the peculiar distribution, although excessive movement in these locations may be a factor.

BULLAE AND ACQUIRED CYSTS OF THE LUNG

The term *bulla* is purely descriptive and has no pathogenetic implications, but it is nevertheless useful if used to describe spaces which are so large that their origins are no longer recognisable. Bullae may or may not be associated with fibrosis of varying degrees and air passages representing various levels of the bronchiolar tree open into them. Sometimes the bronchiolar communications are quite free, whilst in other instances there is a valvular type of orifice and then the space tends to have a smooth and rounded outline. Bullae usually, although not exclusively, occur in association with some form of emphysema.

Bullae and scar emphysema must be considered in relation to cystic states of the lung. The anatomic definition of an acquired pulmonary cyst which we have adopted is an

abnormally large space entirely surrounded by consolidated or fibrotic lung, an extensive example of which is honeycomb lung [*25*]. In this condition the parenchyma is patchily involved by fibrosis or by granulomas, whilst unobliterated lung tissue in the affected areas undergoes cystic dilatation. (Fig. 7.) The fibrous component may arise as a consequence of irregular consolidation, collapse or interstitial fibrosis, and the cysts evidently develop from bronchioles of non-respiratory or respiratory types. Honeycomb lung cannot therefore be distinguished from emphysema on the basis of the distribution of the respective changes in the bronchiolar tree.

This definition of a cyst may be challenged on the ground that there is no clear demarcation between bullae with slight fibrosis in their walls, scar emphysema and cysts, and the choice of term may be made to depend on the extent of the wall composed of fibrous tissue. Widespread fibrosis of patchy distribution may eventually progress to honeycombing, so that scar emphysema may in time be converted into a fibrocystic state. Severe destructive changes in emphysema may result in "empty" (secondary) lobules, occurring singly or in groups, some being traversed by vessels whose lumens are partially or totally obliterated. The walls of the spaces so formed will be composed of fibrous tissue not necessarily newly formed but derived from pulmonary septums and possibly the pleura and, although the lesion is primarily emphysematous, it could ultimately conform to our definition of a cyst. It is quite likely that some large "bullae" are formed in this way and, when such changes involve a segment or a lobe, the lung may be said to have vanished.

The use of the term "bronchiolar emphysema" [*26*] to describe fibrocystic disease of the lung with its characteristic smooth muscle hyperplasia is, according to our definitions, unjustified and should be abandoned.

COMMENTS

Coexistence of Different Types of Emphysema. Focal (i.e., dust) emphysema is characteristically found in coal workers, but these men are also afflicted by other forms of emphysema and those not due to dust may even prove to be as common in coal workers as is the focal variety. Centrilobular and focal forms of emphysema appear to be mutually exclusive in relation to any particular acinus; nevertheless, in a given lung some acini may be affected by centrilobular and others by focal emphysema. Theoretical considerations suggest that, if focal emphysema developed first in an acinus, the walls of the dilated respiratory bronchioles, comprising in effect a thick cylinder of dust enmeshed by fine fibrous tissue, might be strong enough to resist the disruptive effects of a subsequent bronchiolitis, even though the inflammation facilitated dust elimination in some degree. On the other hand, if centrilobular emphysema already existed in a particular acinus, dust deposition might well be impeded and, due to bronchiolar disruption, dust collection could not occur in the way characteristic of focal emphysema. If the causative factors of these two forms of emphysema operated simultaneously, the development of true focal emphysema is likely to be prevented for the same reason. When centrilobular emphysema occurs in coal workers the parent bronchiole and the walls of emphysematous spaces will, however, be pigmented to a variable degree and extent. Slight pigmentation may also occur in town dwellers with centrilobular emphysema, a combination which may partly be responsible for its confusion with focal emphysema. "Vesicular" and focal emphysema may coexist, since they affect different anatomic sections of the airway and, for the same reason, centrilobular and "vesicular" forms may also be associated. Scar emphysema may occur along with any other form.

The Distinction between Focal Emphysema and Centrilobular Emphysema (*Table* II). Failure to make this distinction, as for instance by McLean [*27*] and Wyatt [*28*], has led to confusion of thought on pathogenesis. According to McLean the sequence of events inducing the basic structural changes of emphysema (namely, dilatation of air passages distal to terminal bronchioles with breakdown of the walls) is essentially similar whatever the form of emphysema. He holds that this sequence commences with bronchiolar obstruction by inflammatory exudate (subsequently removed or organised), followed first by trapping of collaterally ventilated air and then by disruption of air passages immediately beyond the obstruction. He further assumes that the obstruction is confined to a terminal bronchiole or a first order respiratory bronchiole. For a number of reasons we cannot accept such an oversimplified view. The evidence of our three-dimensional studies contradicts McLean's assertion that in emphysema

TABLE II

TYPICAL FEATURES DISTINGUISHING TWO FORMS OF EMPHYSEMA AFFECTING RESPIRATORY BRONCHIOLES

	Focal Emphysema	Centrilobular Emphysema
(1) Microanatomy	Respiratory bronchioles surrounded by abnormal amount of dust	Respiratory bronchioles show only normal amount of dust (non-miners)
	All orders of respiratory bronchioles show fusiform dilatation without initial disruption of parenchyma	Respiratory bronchioles of distal order(s) show initial disruption with formation of abnormal spaces
(2) Parent airway	Normal in size	Narrowed, normal or dilated in size
	No inflammatory changes	Bronchiolitis with extension into the emphysematous area
(3) Distribution of lesions	Usually uniformly scattered throughout the lung	Often restricted to large or small areas of the lung

intralobular bronchioles are commonly obliterated and that only non-specific scars remain. Several considerations make it possible to isolate the effects of bronchiolar obstruction from the disruptive element associated with inflammation. Obstruction of respiratory bronchioles or alveolar ducts by plugs of dust-laden cells is occasionally seen in coal workers, but emphysematous changes are not present in distally placed air passages and in these instances there is no inflammatory reaction in the bronchiolar walls. Neither dilatation nor collapse was observed in lung territory supplied by bronchioles (respiratory or non-respiratory) showing simple narrowing [*8*]. Complete blockage of non-inflamed respiratory bronchioles by aspirated mucus has been observed repeatedly in cases of allergic (non-infective) asthma without evidence of collapse or emphysema in the obstructed area [*18*]. Moreover, obstruction is not a feature of focal emphysema or of generalised "vesicular" emphysema; in many instances of centrilobular emphysema the parent bronchioles are not obstructed and when narrowing is evident its degree is not necessarily related to the severity of the emphysema. Taken together, these observations render it most unlikely that simple non-valvular narrowing of bronchioles *per se* is primarily responsible for emphysematous changes. McLean contends that emphysema develops in a restricted zone immediately beyond the alleged obstruction but, on his hypothesis of air trapping, there is no reason why the whole territory beyond a blockage should not be affected. The implication that collateral ventilation is provided only by patent air passages arising from the same stem as a blocked bronchiole [Fig. 10, *27*] is unjustified, since it may be argued that collateral ventilation from adjacent territory supplied by patent bronchioles would nullify the effect of the obstruction.

McLean [*27,29*] criticised Heppleston's [*12*] concept of the pathogenesis of focal emphysema in coal workers on the grounds that (1) it is inapplicable to similar (and more common) lesions containing little or no black pigment, (2) the dilated passages are assumed to be the original although distorted respiratory bronchioles instead of abnormal passages formed after obliteration of original bronchioles, and (3) the part played by permanent inflammatory damage was not considered. These criticisms are without foundation. The first and third objections arose because McLean failed to differentiate the focal and centrilobular forms of emphysema (as here defined) from each other and from scar emphysema, and in fact made passing reference to the changes in only two coal workers. Inflammatory damage to bronchioles is a primary feature of centrilobular but not of focal emphysema. In a three-dimensional comparison between coal workers, in whom the degree of focal emphysema ranged from nil to severe, and normal subjects, there was no evidence that respiratory bronchioles were obliterated by dust accumulation [*8*], thereby contradicting McLean's second criticism. Whilst McLean's account reveals the existence of centrilobular emphysema in Australia, Badham and Taylor [*30,31*] had previously recognised a form of emphysema localised to the immediate vicinity of dust collections in the lungs of Australian coal workers.

The Pathogenesis of Emphysema. In discussing the pathogenesis of emphysema it is important

to distinguish primary and secondary factors, so far as the evidence permits. The factors we believe may be *primarily* concerned have already been indicated and need only be summarised. Deficiency of muscle in the bronchial tree or possibly abnormalities of the thoracic cage may form the basis of generalised "vesicular" emphysema by leading to fixation of the thorax in a position of partial inspiration. Immobilisation of alveolar structures and atrophy of bronchiolar smooth muscle appear to underlie the genesis of focal emphysema. Anatomic disruption is a primary event in centrilobular and in irregular emphysema, but immobilisation of lung tissue, often by fibrosis, also plays a part in these two forms and this latter effect will be augmented by the subsequent contraction of fibrous tissue. Inspiratory movement evidently contributes to the genesis of several varieties of emphysema.

Once a particular type of emphysema is established its severity may increase from the continued operation of the primary factor(s) and also on account of the participation of *secondary* factors. When anatomic disruption occurs in focal or generalised "vesicular" emphysema it does so only in the more advanced stages and it may become the most important cause of further progression. Disruptive emphysema may supervene because alveolar walls have undergone slow atrophy or have suddenly ruptured (from mechanical or inflammatory causes), but two considerations suggest that the former process is the more likely. First, when disruption begins in "vesicular" emphysema, the uniform pattern of change, typifying the disease up to this stage, is still evident. Secondly, the early stage of breakdown in such cases takes the form of small defects in alveolar walls. These holes, which have long been recognised in emphysema [*32–34*], possess smooth, rounded outlines. Coincidentally with the development of defects, the capillary bed of remaining alveolar tissue appears to be diminished and, although it is difficult to distinguish cause and effect, it may well be that a progressive loss of capillaries in the initial atrophic process eventually leads to dissolution of alveolar tissue. It must be remembered that alveolar walls are largely composed of capillaries.

Emphysematous changes, whatever their type, are often more severe in the upper than in the lower parts of the lung and this also applies to bulla formation. Diminished ventilation and perfusion in the upper zone as compared with the lower [*35–37*] may possibly account for this variation in severity. Dock pointed out that in adult man in the erect position the pulmonary arterial flow is relatively diminished in the upper third of the lung. Hence in this area gaseous exchange may be less, and therefore that fewer antibodies and phagocytes will arrive, whilst removal of bacteria or their products is likely to be impaired. Reduced perfusion and ventilation evidently do not cause permanent damage to capillaries in the upper zone of normal lungs, but when the capillary bed is diminished as a result of emphysema the existing atrophic or disruptive processes may well be aggravated. Furthermore, the physiologic disparities suggest that the reactions to inflammation may not be the same throughout the lung. Consequently emphysematous disruption in the upper part may become more severe either from direct damage or following vascular obliteration. The tendency for emphysematous disruption to involve peripheral rather than central areas of the lung may have a mechanical explanation. Transmission of inspiratory movements to the centre of the lung must occur through its more peripheral parts, which may thus experience a greater strain as the pulmonary resistance to expansion is being overcome.

Dayman [*38,39*] has shown that, unlike the tension in simple, hollow, elastic or semielastic structures, lung tension normally rises progressively as lung volume increases, a feature which evidently depends on the complexity of lung structure. Dayman also points out that in emphysema the lung tension is diminished. Any breach in structural continuity necessitates a local readjustment of lung tension and here the experiments of Moolten [*40*] are pertinent. He produced gross defects bronchoscopically in isolated, unopened human and calf lungs, which were then expanded under negative pressure. Rounded spaces of smooth outline developed at the sites of the artificial defects and the sizes of the spaces varied in proportion to the degree of expansion of the whole lungs. In the production of the spaces Moolten stressed two main factors, disruption of the framework of the lung and expansion of the organ. It would appear that a space ceases to enlarge when tension at its margin equals that of ambient lung. Thus, in the production of abnormal spaces, atmospheric pressure, transmitted through the air passages, can be adequate, although in emphysema the size of spaces resulting from disruption may well be

increased when tension in surrounding lung is diminished, as for instance by "vesicular" emphysema.

Loss of lung tension is evidently reflected by the physiologic changes, which indicate a greatly increased airway resistance during expiration in emphysema [*38,39*]. To account for this, Dayman advocates the hypothesis of an expiratory check-valve obstruction. He believes that such a mechanism is secondary to loss of lung tension from anatomic disruption and represents an exaggeration of the normal tendency in regard to intrathoracic air passages. Cough and structural narrowing of air passages evidently increase the efficiency of the check-valve mechanism [*39*]. An abnormally high pressure may be obtained within an area of disruption [*41*]. This may be explained by assuming that such an area has a check-valve communication with bronchiole(s) and that the positive pressure is achieved by forced expiration. It is, however, difficult to believe that during expiration air is diverted within the lung from areas of normal tension into areas of reduced tension. Expiratory pressure should be evenly distributed throughout such lungs, provided they are enclosed in the thorax [*42*].

It has been suggested that inspiratory air flow, especially that preceding cough, may influence the progression of emphysema [*43,44*]. If some bronchioles are narrowed it is postulated that ventilation of the territory they supply is diminished, whilst compensatory overventilation occurs in ambient normal lung connected with unobstructed air passages. In centrilobular emphysema the anatomic evidence contradicts this view since the emphysematous spaces connect with diseased bronchioles. We have no evidence to say whether the postulated mechanism participates in other varieties of emphysema.

Whilst these considerations are somewhat speculative, they serve to stress the need for an experimental approach. It is, nevertheless, worth reiterating that the evidence as a whole strongly suggests that physiologic obstruction to air flow is a consequence and not a primary cause of emphysema.

Vascular Changes in Emphysema. The state of the pulmonary circulation is difficult to judge postmortem. Assessment of the size of vascular lumens in different zones demands a carefully standardised technic. Frequently there is obvious loss of capillary bed and an idea of the vascular dispositions may be gained by injection technics. The bronchopulmonary circulatory relationships are severely disturbed in emphysema. Liebow [*45*] has demonstrated a striking increase in the venous collateral system, whereby the normal shunts between pulmonary and systemic vessels were considerably enlarged, and also a less prominent expansion of the bronchial arterial circulation. As yet, however, there is no certain means of judging whether the available channels were used during life and, if so, in which direction blood flowed. Pressure relationships have not been measured and can only be inferred [*46*]. It is nevertheless worth noting that in our cases of generalised "vesicular" and of focal emphysema the pulmonary arterioles accompanying the terminal and respiratory bronchioles showed no consistent evidence of endarteritic or thrombotic stenosis. In those cases of centrilobular emphysema showing endarteritis the degree of vascular stenosis did not parallel the degree of emphysema and there was no quantitative relationship between the severity of the endarteritis and that of the bronchiolitis. The available evidence leads us to believe with Liebow [*46*] that vascular changes do not constitute the essential basis of emphysema but, when present, are secondary manifestations.

SUMMARY

Reasons are given for relying on micro-anatomy in the definition and classification of chronic pulmonary emphysema. The distinguishing anatomic features of different forms of emphysema are presented and their pathogenesis is discussed in regard to the participation of primary and secondary factors. An attempt is made to relate structural change to physiologic observations.

Acknowledgment: Figures 1 and 2A are reproduced from HEPPLESTON, A. G. *J. Path. & Bact.*, 66: 235, 1953 [*8*].

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Clinicopathologic Conference

A Six-Month Illness with Spiking Fever, Pancytopenia, Hypoproteinemia, Splenomegaly and Salmonella Organisms in the Stool*

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient's first admission to the Barnes Hospital was on February 4, 1960. Two and a half months prior to admission, this seventy year old white housewife noted generalized fatigue. Six weeks prior to admission she had daily spikes in temperature to approximately 101° to 102°F. She was treated with antibiotics but continued to have recurrent episodes of fever in the afternoon, unaccompanied by chills or sweats. She had no cough, hemoptysis or chest pain, but noted an increase in some long-standing postprandial nausea and belching. An unknown amount of weight loss occurred, but without abdominal pain, jaundice or dark urine. Her stools were normal in color and were free of blood.

The patient stated that she was allergic to aspirin and sulfa drugs. In 1920 she suffered an attack of "gallstone colic" with a brief bout of jaundice from which she recovered without lasting ill-effect. In 1937 she once more noted jaundice, which was reported to have lasted for a year. She then had swelling "all over the body," was treated with digitalis, and the swelling disappeared. She did well until 1939, when she had "typhoid fever" and recurrent jaundice; she was ill for approximately six months. An almost constant complaint for many years had been postprandial abdominal distress, particularly after eating cabbage.

On physical examination the blood pressure was 100/50 mm. Hg, temperature 37.5°C., pulse 88 per minute and respirations 20 per minute. The patient was a slightly obese, elderly white woman in no acute distress. Her skin was pale with scattered areas of increased pigmentation, especially over the extremities. There was a small, slightly tender, elevated lesion beneath the tongue, and a soft, round, non-tender nodule overlying the thyroid cartilage. There was dorsal kyphosis and an increase in the antero-posterior diameter of the chest. Breath sounds were of good quality. The left border of cardiac dullness was just beyond the left mid-clavicular line. There was a grade 1 apical systolic murmur. The tip of the spleen was felt 1½ finger-breadths below the left costal margin and was slightly tender. No other organs or masses were felt. The neurologic examination was within normal limits.

Laboratory data revealed the following: hemoglobin 9.5 gm. per cent, hematocrit 29 per cent, white blood cell count 2,700 per cu. mm. with a differential of 52 per cent segmented forms, 2 per cent stabs, 40 per cent lymphocytes and 6 per cent monocytes. There were 9 per cent reticulocytes. The red blood cells were normochromic and normocytic. Corrected sedimentation rate was 26 mm. per hour. Urinalysis revealed a specific gravity of 1.017, pH 5, albumin and sugar negative; microscopic examination of the centrifuged urinary sediment revealed 4 to 6 renal epithelial cells and a few white blood cells. Stool guaiac and blood Kahn

* Manuscript received April 4, 1961.

reactions were negative. Results of fasting blood sugar, blood urea nitrogen, calcium, phosphorus, cholesterol, amylase, transaminases, prothrombin time, cephalin cholesterol flocculation, thymol turbidity, and van den Bergh tests were normal or negative. Alkaline phosphatase was 6.1 Bodansky units, and the total protein was 4.8 gm. per cent with an albumin:globulin ratio of 2.9:1.9. Direct platelet count was 65,000 per cu. mm.

Roentgenographic examination of the chest revealed osteoporosis, kyphoscoliosis, emphysema, bilateral basilar pneumonitis, a lobulated right diaphragm and bilateral calcific tuberculosis. A hiatus hernia was discovered on roentgenographic examination of the upper gastrointestinal tract. Lower gastrointestinal series did not reveal any abnormalities. The gallbladder was only faintly visualized after a double dose of Telepaque.® The electrocardiogram was within normal limits. Multiple blood cultures were negative. Agglutinations for salmonella, brucella and proteus OX-19 were negative. Latex agglutination was weakly reactive.

For a few days after admission daily temperature spikes between 38.5° and 39°C. were noted. Because a culture of stool revealed type E salmonella, the patient received Chloromycetin® for ten to eleven days. Coincident with the beginning of this treatment her temperature became essentially normal; however, after a few days the daily temperature spikes recurred. Sensitivity studies having shown the salmonella organism to be sensitive to tetracycline, Chloromycetin therapy was discontinued and tetracycline therapy was begun. This was continued for about two weeks; during this time the salmonella organisms disappeared from the stool. However, since the fever persisted, tetracycline therapy was discontinued and kanamycin therapy begun. Shortly after the institution of kanamycin therapy, a diffuse maculopapular skin rash developed and results of liver function tests became abnormal (cephalin cholesterol flocculation 3 plus, thymol turbidity 3.3, van den Bergh: direct 0.3 mg. per cent, indirect 0.8 mg. per cent, alkaline phosphatase 4.1 Bodansky units). The blood urea nitrogen rose to 42 mg. per cent. The urinary sediment contained many granular casts and hyaline casts, many white blood cells, renal epithelial cells and a few red blood cells. Intravenous pyelograms at this time revealed poor concentration of dye bilaterally. The rash, abnormal reaction to liver function tests and renal abnormalities all disappeared following cessation of kanamycin therapy.

Examination of bone marrow revealed erythrocytic hyperplasia of moderate degree, with normal myeloid and megakarocytic elements. Because of the patient's continuing moderate abdominal tenderness and evidences of hypersplenism, splenectomy was performed on March 25. Pathologic examination of the spleen revealed hemosiderosis, erythrophagocytosis and scattered areas of mild fibrosis. Following operation the patient did well and was virtually afebrile until the fourth postoperative day when her temperature reached 38.5°C. in the afternoon. Thereafter, the temperature spiked each day to higher levels, reaching 39.6°C. on the ninth hospital day.

Fluoroscopy revealed both diaphragms to be moving well; a question of pneumonitis at the base of the left lung was raised. The temperature was controlled with salicylates and other symptomatic therapy. Tetracycline treatment was resumed, and continued until the time of the patient's discharge. Until that time the patient continued to have moderate, vague abdominal distress, tachycardia, malaise and weakness. She was sent home for convalescent care on April 11, 1960.

Two days after discharge diarrhea, abdominal pain, chills, fever, nausea and vomiting occurred. The patient began to cough, without the production of sputum. She became confused and incontinent of urine. She was re-admitted three days later (April 15, 1960).

On physical examination the temperature was 38.7°C., blood pressure 97/60 mm. Hg, pulse 140 per minute and respirations 25 per minute. The skin was dry; there was poor turgor. Patchy areas of increased pigmentation were noted as before. Skin around the palms and soles revealed a patchy, macular eruption. Cheilosis was noted. The tongue was red and smooth. There were areas of thick white exudate in the pharynx. There was dullness to percussion over the lower third of the left lung field; no breath sounds could be heard over this area. The remainder of the lung fields were clear to percussion and auscultation. The left border of cardiac dullness could not be determined. The abdomen was slightly distended. The patient complained of tenderness in the upper left quadrant and to a lesser extent in the upper right quadrant. No organs or masses could be felt, nor could a fluid wave

be elicited. There was 3 plus edema of the ankles. Peripheral pulses could not be felt in the feet. There was generalized muscle weakness. Neurologic examination did not reveal any abnormalities.

Laboratory data were as follows: Hemoglobin 15.5 gm. per cent, hematocrit 48 per cent, white blood cell count 22,550 per cu. mm. with a differential of 75 per cent segmented forms, 4 per cent stabs, 15 per cent lymphocytes and 6 per cent monocytes, platelets 163,000 per cu. mm. reticulocytes 2.6 per cent. Erythrocyte sedimentation rate was 1 mm. per hour. Urinalysis revealed a specific gravity of 1.010, pH 5, protein and sugar negative; microscopic examination of the urinary sediment was within normal limits. Stool guaiac and blood Kahn reactions were negative. The fasting blood sugar was 141 mg. per cent, blood urea nitrogen 40 mg. per cent, cholesterol 136 mg. per cent, prothrombin time 48 per cent, cephalin cholesterol flocculation 3 plus, thymol turbidity 2.4, van den Bergh: total bilirubin 5.6 mg. per cent, direct 3.4, indirect 2.2. The serum glutamic oxalocetic transaminase was 104 units, serum glutamic pyruvic transaminase 21 units, alkaline phosphatase 26 Bodansky units, albumin 1.7 gm. per cent, globulin 1.9 gm. per cent, sodium 133 mEq. per liter, potassium 3.7 mEq. per liter, chloride 93 mEq. per liter, and carbon dioxide 26.5 mEq. per liter. Results of Coombs' tests, direct and indirect, were negative; latex agglutination was reactive; and salmonella agglutinations were negative. Bromsulphalein retention was 38.2 per cent in forty-five minutes; protein-bound iodine was 4.4 μg. per cent.

The venous pressure, circulation time and electrocardiogram were within normal limits. Stool culture revealed no pathogens. Multiple blood cultures were negative. Reactions to tuberculin skin tests were negative. Lumbar puncture revealed normal pressure; examination of the spinal fluid revealed 1 cell per cu. mm., protein 43 mg. per cent, sugar 64 mg. per cent, chloride 113 mg. per cent. Colloidal gold and Wassermann reactions were negative.

At thoracentesis of the left side of the chest, 250 cc. of serosanguinous fluid were removed without difficulty. Examination of the fluid revealed a specific gravity of 1.007, 2,250 white blood cells per cu. mm., 137,000 red blood cells per cu. mm., albumin 0.9 mg. per cent, globulin 0.4 mg. per cent and cholesterol 36 mg. per cent. Routine cultures and cultures for acid-fast bacilli were negative. Roentgenographic examination of the chest revealed an increase in the pleural effusion bilaterally, with bilateral infiltration of the lower lobe, as before. The patient was begun on tube feedings and was given hypertonic glucose solution and human serum albumin intravenously. Following the intravenous administration of albumin and therapy with mercurial diuretics the edema cleared rapidly.

A few days after admission, the right submaxillary gland became swollen, warm and tender. Purulent drainage appeared at the orifice of this gland. Culture of this drainage revealed a heavy growth of yellow staphylococcus and Escherichia coli. Fungus cultures revealed Candida albicans.

During the patient's hospitalization her cough became more and more prominent. She began to produce copious amounts of thick, purulent sputum requiring frequent tracheobronchial suctioning. Although her nutritional status seemed to improve, and the results of liver function tests became less abnormal, her general condition deteriorated constantly. Multiple decubitus ulcers developed and, a few days before death, extreme tachypnea. Roentgenographic examination of the chest at that time revealed only the bilateral pleural effusions as before, and mottled infiltrates in both lower lobes.

On the day of death the patient had progressively more difficulty clearing her tracheobronchial secretions. She died on May 10, 1960, with what appeared to be obstruction of the upper respiratory tract.

CLINICAL DISCUSSION

DR. SOL SHERRY: Except for some ill-defined bouts of jaundice in her middle age, this patient apparently was healthy until the age of seventy when an illness developed which led to her death six months later. This illness began with the onset of generalized fatigue, but, after several weeks, daily temperature spikes and weight loss occurred. The fever was unresponsive to antibiotic therapy, and she was hospitalized for the first time approximately two and a half months after the onset of her illness. Work-up at that time revealed fever, pancytopenia, hypoproteinemia and splenomegaly. Since salmonella type E organisms were cultured from the stool, it was believed, initially, that she had an enteric fever. Later, attention focused on

her dysplenism, and a splenectomy was performed. Although the pancytopenia responded to the removal of the spleen, her clinical condition soon worsened and it was feared that a subdiaphragmatic abscess had developed. Finally, she seemed to be improving, and was sent home to convalesce.

However, three days later she was readmitted. In the interim, diarrhea, abdominal pain, chills, fever, nausea, vomiting and cough had developed. From this point on her illness was dominated by severe malnutrition, hypoproteinemia, decubitus ulcers and progressive suppurative infections involving the right submaxillary gland and both lungs. On the last day of her illness marked tachypnea developed, followed by labored breathing and death.

Dr. McAlister, will you present the roentgenographic findings?

DR. WILLIAM H. MCALISTER: The gastrointestinal series showed a small, sliding hiatal hernia with gastroesophageal reflex. The stomach, small bowel and colon were intrinsically normal. There was no evidence of hypertrophy of the gastric folds or of an abnormal small bowel pattern. A large spleen displaced the stomach, splenic flexure and left kidney. An oral cholecystogram revealed four moderate-sized radiolucent calculi and poor concentration of the contrast material. The intravenous pyelogram was normal except for displacement of the left kidney by the spleen.

A lateral roentgenogram of the lumbar spine showed diminished bone density, accentuation of the end plates, trabecular thinning, some biconcave vertebrae and compression fractures.

The initial chest roentgenograms revealed an increase in the anteroposterior diameter of the chest, dorsal kyphosis, diminished bone density and a normal cardiovascular silhouette for this age. There was a fine reticular pattern in the lower lobe of the left lung. The upper lobe of the right lung contained a small calcified granuloma.

The remaining chest roentgenograms were taken after splenectomy. The left hilus was depressed. Partial collapse of the lower lobe of the left lung with left pleural effusion was present. Several days later both the amount of collapse and the left pleural fluid increased. The right lung still appeared normal. The last roentgenograms were taken three weeks later, or one day prior to death. Although left pleural effusion had decreased, a sizable infiltrate had appeared in the lower lobe of the left lung, lingula and anterior segment of upper lobe of the left lung. Some partial collapse of the lower lobe was present. The large gas-filled splenic flexure would be against any sizeable mass in the upper left quadrant. The heart size had not increased; the pulmonary vascularity looked normal. Since the last examination three weeks earlier, a decrease in volume, a large amount of infiltrate and a moderate-sized pleural effusion had developed in the lower lobe of the right lung. The rapidity of the process, particularly on the right, I think would speak against neoplasm.

DR. SHERRY: Would it also be a point against granulomatous disease?

DR. MCALISTER: I would think so.

DR. SHERRY: Since the pulmonary findings came on late in her course, do you interpret them as most likely representing a complication or late manifestation of her illness as opposed to some primary process initially involving the lungs?

DR. MCALISTER: I would think so.

DR. SHERRY: Dr. Saltzstein, would you describe the pathologic condition of the spleen removed at laparotomy?

DR. SIDNEY SALTZSTEIN: We received a spleen which weighed 560 gm. This is two to three times normal size. Externally it was normal. On section it had dark red pulp. The follicles were relatively inapparent. Unfortunately, no lymph nodes were present in the hilum of the specimen; frequently these are of more use to us in establishing a diagnosis than the spleen itself.

The malpighian bodies were relatively inapparent grossly, as they were quite small. On higher power observation there was evidence of hemosiderin deposition and phagocytosis of erythrocytes. There was some increase of fibrosis. That is about as far as we were able to go. We saw no evidence of any specific disease.

DR. SHERRY: If this patient's illness were due to an infectious process associated with disseminated granulomas, would one invariably expect to find granulomas in the spleen, particularly when it is enlarged to the extent observed here?

DR. SALTZSTEIN: When one has that much of a granulomatous disease, one should find evidence of it in the spleen. I cannot say that it will always be there, but my experience is that one does find it.

DR. SHERRY: Is there any evidence to suggest that the splenic disorder could be on a congestive basis?

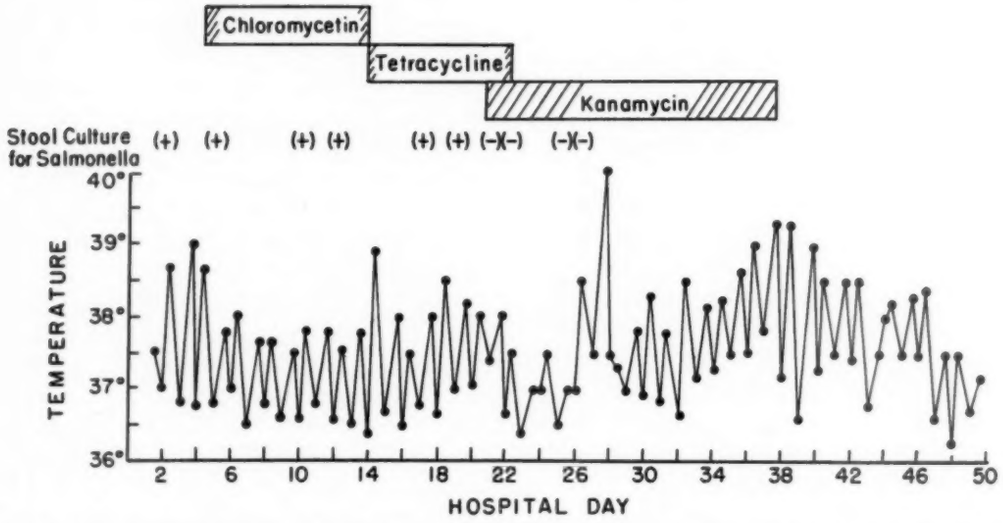


FIG. 1. Temperature course, cultural data and antibiotic therapy during first fifty days of hospitalization.

DR. SALTZSTEIN: Fibrosis, as seen here, is frequently attributed to long-standing congestion of the spleen, and possibly this case could be interpreted that way. We saw no vascular congestion *per se*, but this would depend upon such things as whether the vein or the artery was tied first in surgery and how much blood escaped when we cut the sections.

DR. CARL G. HARFORD: Was the spleen cultured?

DR. SALTZSTEIN: No, it was not. However, we saw no evidence of any inflammatory process.

DR. SHERRY: Dr. Wiegand, you followed this patient in the hospital and performed several bone marrow aspirations. Would you comment on the bone marrow findings and any other observations made at the time of surgery?

DR. HERBERT WIEGAND: The hematologic picture which we found in this patient upon admission was that of pancytopenia with a red blood cell count of 2.3 million per cu. mm., 9 per cent reticulocytes, a white blood cell count of 3,100 per cu. mm. and a platelet count of 60,000. The bone marrow showed a full supply of all the cellular elements, erythroid, myeloid and megakarocytic. Our initial thought about the peripheral count was that some of it could have been due to depression from a chronic infection, because we had found the salmonella enteritis. As we followed the case and as the salmonella enteritis cleared, we found no change in the count. We came to the conclusion that, at least from a functional standpoint, there was good evidence of hypersplenism. Dr. Lischer, therefore, performed a splenectomy. Due to the fact that the patient had numerous petechiae and ecchymoses and did present a bleeding problem, he was considerably disturbed at carrying out an extensive exploration. He therefore limited his work to a splenectomy; went in and out as fast as he could. He was very reluctant to take any lymph node biopsy specimen in the abdominal cavity or a liver biopsy specimen, which we wanted if at all possible.

DR. SHERRY: The operative note simply reports that all the organs felt normal.

DR. WIEGAND: That is right. We did not feel an enlarged liver during this stage; however, the spleen was large and palpable.

DR. SHERRY: The first thing we need to establish is whether the patient indeed had an enteric fever with a salmonella organism.

The initial course of this patient at the time of her first admission is summarized in Figure 1. As you will note, the patient entered the hospital quite febrile, with a temperature varying between normal and 39°c. On the third hospital day the stool culture grew out a salmonella type E organism. At this time a urine culture also showed 100 colonies of salmonella E, but since this was grown from a clean voided specimen, it is impossible to tell whether the organism might have come from the stool. The patient was given Chloromycetin for approximately eight days. Associated with the administration of Chloromycetin, the temperature fell progressively and approached a normal range, but did not become completely normal. Since the stool cultures

remained positive it was decided to switch antibiotics; on the basis of sensitivity tests, a tetracycline compound was chosen. Achromycin® was then given for the next seven days, during which time the salmonella organism disappeared. However, since the patient again became febrile, it was decided to switch to kanamycin therapy. On kanamycin therapy, over a period of approximately eleven days, the stool cultures remained negative, but the febrile course persisted.

Dr. Harford, would you evaluate the salmonella infection for us? Was this simply a carrier state, a salmonella enteritis or a true enteric fever?

DR. HARFORD: I have a few more facts to add. If I remember correctly, the urine culture of this patient was obtained before the stool culture, and the presence of salmonella suggested the need for stool cultures. The salmonella was isolated from the stool on six occasions, sometimes in a heavy growth, and each time was agglutinated by group E antiserum. A subculture of the strain obtained from the urine was sent to the St. Louis Health Division for further identification and was reported to be salmonella give. Reference to *Bergey's Manual* indicates that this type is in group E_1; that is, it has somatic antigens 3 and 10. The flagellar antigens are also given. This type is an unusual one, but there are about four hundred types of salmonella now, and I think we should expect unusual ones occasionally.

In the laboratory, we were disturbed by the fact that the serum of the patient failed consistently to agglutinate a suspension of group E salmonella treated appropriately to reveal 0 agglutination. The organism isolated from the patient was only partially agglutinated by her serum in a dilution of 1:20. This apparent poor antibody response caused us to suspect that the patient may have been a poor antibody producer and suggested the possibility of hypogammaglobulinemia.

As to the clinical significance of the salmonella, I think that the fever, palpable spleen, leukopenia and the frequent presence of the organism in large numbers make it difficult to exclude the possibility that the patient may have had the enteric fever syndrome often seen in salmonella infections. I do not think it helps to know what group or type of salmonella was present because, although some types cause enteric fever more commonly than gastroenteritis, most of them can induce either type of clinical disease. The fact that the fever disappeared for a few days following therapy with chloramphenicol is suggestive, but the temperature became normal even more rapidly than I would expect. In patients with typhoid fever treated with chloramphenicol, it takes about three days for the fever to subside. The fact that the organism persisted despite therapy with chloramphenicol is not inconsistent with the diagnosis because therapy with this drug is not eradicative, at least not after the period of time in which it was administered to this patient. On the other hand, the effect of chloramphenicol on the clinical manifestations and fever of typhoid fever seems to me to be more clearly established than in the case of tetracycline drugs. Later in the course of this patient's illness, diarrhea occurred, and may have been a gastroenteritis caused by salmonella. In some cases of salmonella infection, the syndromes of enteric fever and gastroenteritis may occur in the same patient.

The duration of fever in this patient before she came to the hospital was longer than I would expect in a usual case of salmonella fever. She had anemia on admission and this finding also suggests a process of some duration. Therefore, in addition to the possibility that she had an enteric fever syndrome caused by salmonella, I think we should consider the possibility that she had some other underlying disease and that salmonella were present because she was a carrier.

DR. SHERRY: It would be extremely important for us to determine whether she had an enteric fever or not; if she did, many of the findings in this case could be explained. Patients with enteric fevers may run a protracted febrile course, and considerable debility, extensive weight loss and even dysplenism may develop.

DR. HARFORD: We may add also that the patient had pulmonary lesions and that salmonella pneumonia is a well known entity.

DR. SHERRY: Dr. Garfinkel, does the possibility of a salmonella enteric fever seem attractive to you?

DR. BERNARD GARFINKEL: I certainly have little more to add to Dr. Harford's discussion of the over-all problem. There is one other aspect of salmonella infection, a variant of the enteric fever syndrome, into which this patient fits a little better. This is the picture of chronic, long-standing, recurrent disease with recurrent fever, the development of lymphadenopathy, spleno-

TABLE 1

Date	White Blood Cell Count (per cu. mm.)	Hemoglobin (gm./100 ml.)	Hematocrit (per cent)	Red Blood Cell Count (millions per cu. mm.)	Platelets (per cu. mm.)
2/4/60	2,700	9.5	29	...	...
2/6/60	3,250	9.0	25	...	65,000
2/15/60	2,800	9.7	...	...	...
3/2/60	4,000	10.2	...	...	...
3/3/60	3,100	8.4	27	2.35	60,000
3/18/60	4,600	7.9	24	2.20	52,000
3/22/60	8,400	7.8	24	2.29	53,000
3/25/60	*After Splenectomy and Transfusions*				
3/28/60	12,100	11.8	38	3.64	102,000
4/5/60	8,800	11.6	43	3.71	104,000
4/15/60	25,500	15.5	48	...	163,000
4/20/60	17,300	11.1	36	3.67	81,000

megaly and hepatosplenomegaly. In many of these instances the organism is not easily cultured; it may be found only in the bone marrow or in lymph nodes. In this form of infection, bone lesions or lung lesions are frequently found. I think this entire case could be explained on the basis of that type of salmonella infection rather than the usual picture of enteric fever as we usually see it.

DR. SHERRY: Is there actual involvement of the small intestine in this form of salmonella infection?

DR. GARFINKEL: There may be, yes.

DR. SHERRY: Severe enough to develop an enteropathy which might account for the hypoproteinemia?

DR. GARFINKEL: There is involvement certainly of the lymphatic tissue of the small bowel. I have had one case in a man who seemed to have Hodgkin's disease clinically. He had anemia, leukopenia, relapsing fever, marked lymphadenopathy and hepatosplenomegaly. This man was eventually found to have a salmonella C-1 infection. The organism was cultured from his bone marrow, and numerous blood cultures were negative. He subsequently was treated with chloramphenicol with an excellent initial response. Six months later he had a relapse and the clinical course was the same. Salmonella C-1 was cultured from his bone marrow a second time. I think this type of infection certainly could explain this patient's entire course.

DR. SHERRY: From the information we have, all we can conclude is that this patient may or may not have had a significant salmonella infection, and its relation to the pathogenesis of her illness remains obscure. Now let us turn to the dysplenism which the patient exhibited. Dr. Reinhard, are you willing to accept the presence of a dysplenism; if so, do we have sufficient data to distinguish whether it was a primary or secondary form?

DR. EDWARD H. REINHARD: I would like to point out several things that perhaps have not been emphasized in the previous discussion. (Table 1.)

Although this patient certainly did have pancytopenia when she was first seen, the white blood cell count had returned to normal prior to splenectomy. During the month of March, the patient received antibiotic therapy on the assumption that she had a salmonella infection and that the fever was probably due to this infection. Might not the leukopenia have been due to the salmonella infection? This is a common blood finding in salmonella infections, and with effective treatment the white blood cell count does return to normal. Frequently in salmonella infections, during the later course of the disease, if there are septic complications of the disease leukocytosis does develop. Hence, I do not believe, on the basis of the data in this case, that we can say that the spleen was directly implicated in the pathogenesis of the original leukopenia.

As far as the platelet count is concerned, you will see that the patient had persistent thrombocytopenia, the bone marrow showed adequate

megakarocytes, and the platelet count did improve somewhat following splenectomy. Again, however, the evidence that the platelet depression was primarily due to a splenic mechanism is not terribly convincing because you can remove the spleen from a perfectly normal person and the platelet count will increase proportionately as much as it did in this case. And you will also note that subsequently the platelet count went down again almost as low as the original value, even though the patient's spleen was out.

We come then to the anemia, and here it would seem that we have much more convincing evidence of a splenic mechanism. The patient had marked anemia with a bone marrow containing large numbers of erythroid cells, and there was a very significant reticulocytosis. At the time of splenectomy the patient's hemoglobin was restored to normal by, I believe, three blood transfusions. Following splenectomy, despite the fact that the patient was quite ill, she seemed to maintain her hemoglobin level fairly satisfactorily. I could not find any definite evidence that she received a transfusion between April 5 and April 15. At any rate, the reticulocyte count remained at a much lower level after splenectomy than it had been before. Therefore, I believe there is fairly good evidence that the spleen was in some way participating in the destruction of red cells, and that this factor at least was benefited by splenectomy.

Another way of looking at this would be that this patient had a profound disturbance of the entire reticuloendothelial system, that the spleen was involved to the extent that the spleen is the largest single mass of reticuloendothelial tissue and this could then have been a fairly non-specific splenic mechanism. In other words, with a chronic granulomatous infection, the spleen is often involved. I am very much disturbed by the fact that the spleen did not show granulomatous lesions, as it usually does in diffuse granulomatous infections. I still think, however, that a satisfactory way to look at this would be that this patient had a chronic granulomatous infection, with the usual profound effect on the reticuloendothelial system, with an increase in the number of plasma cells and reticulum cells in the reticuloendothelial tissues, and perhaps increased phagocytosis, particularly of red cells. This latter effect was apparent in the spleen, but I think it may also have been taking place in other organs. In other words, I am not sure there was any specific disease in the spleen; the disturbance in the spleen may merely have been part of a more generalized disease or disturbance in the reticuloendothelial system secondary to a chronic granulomatous infection such as salmonella.

DR. SHERRY: Does the presence of moderate leukopenia either in association with dysplenism or other disease diminish immunity to infection?

DR. REINHARD: I think that leukopenia has some effect in interfering with a resistance to infection, but as a rule the relatively mild leukopenia that accompanies a salmonella infection such as we see here, probably does not play any important part in resistance to infection.

DR. SHERRY: Although you seem primarily attracted to a chronic granulomatous infection, and particularly with a salmonella organism, you do admit that the evidence is non-specific for some disease diffusely involving the reticuloendothelial system. Under these circumstances, should we give serious consideration to an entity like Hodgkin's disease?

DR. REINHARD: That is a difficult diagnosis to make in a patient who has a known salmonella infection. I think that even when you make the diagnosis of Hodgkin's disease in a patient who has had six or eight stool cultures positive for salmonella you would be wrong ninety-nine times out of one hundred. However, you cannot exclude the diagnosis.

DR. SHERRY: Dr. Loeb, do you agree with Dr. Reinhard's interpretation?

DR. VIRGIL LOEB, JR.: I would agree with what Dr. Reinhard has said with reference to the dysplenism. Since the microsections of the spleen are so non-specific, it would be difficult to incriminate a lymphoma; at least, if such a disease existed it apparently did not involve the spleen. I believe that this probably reflects a secondary or "symptomatic" dysplenism rather than a primary disease of the spleen.

DR. SHERRY: What about some obscure neoplasm? Could a neoplasm induce a syndrome like this without directly infiltrating the spleen? We have certainly seen some interesting patterns develop in patients with neoplasms.

DR. LOEB: Yes, but it would be difficult to explain the splenomegaly on the basis of an obscure neoplasm, unless you are assuming that the enlarged spleen is related to the salmonella infection and that there is a coexistent neoplasm.

DR. SHERRY: No, I meant that an obscure neoplasm may set in motion a train of events

which leads to abnormal splenic function, which then takes the pattern of a dysplenism.

DR. LOEB: There is evidence that a neoplasm may evoke hemolytic anemia, leukopenia or thrombocytopenia by virtue of antibody formation at the site of the tumor, but to imply that a large spleen of 540 gm. might develop as the result of a latent or an inapparent neoplasm somewhere in the body would be difficult to justify.

DR. SHERRY: And you are not attracted to the possibility that this could be primary hypersplenism?

DR. LOEB: No, I do not believe there is sufficient evidence. I would like to emphasize one remark made by Dr. Harford; namely, that hypogammaglobulinemia might play a role here. I think this is a possibility, even though the globulin was reported as 1.9 on two occasions. Electrophoretic patterns might have shown an absolute decrease in gammaglobulin level and thereby explain the negative reaction to the Coombs' test and the negative agglutination titers.

DR. SHERRY: You have described a thymoma which was associated with splenomegaly and hypogammaglobulinemia. Should we consider this possibility here?

DR. LOEB: Since we have seen examples of this, I suppose it should be considered although we have no reason to suspect it seriously in this patient.

DR. REINHARD: I think it might be interesting to mention that hemolytic anemias do occur fairly commonly in association with a variety of infections, and these are in general the granulomatous infections. For example, in Clostridium welchii and Vibrio cholera septicemia, hemolytic anemia, which may be very severe, occurs rather consistently. Furthermore, hemolytic anemia occurs in association with typhoid fever. We certainly see it in association with the other salmonella infections. I have seen several cases of hemolytic anemia in which the hemolytic anemia and fever were the initial manifestations of the salmonella infection. In one of these, a patient who had extensive disease outside the gastrointestinal tract, a salmonella osteomyelitis developed. Ultimately the patient ended up with extensive destruction of the head of the femur, which was proved to be due to a salmonella bone infection. She had very severe hemolytic anemia with a positive reaction to the Coombs' test. The result of the Coombs' test is often negative in hemolytic anemia associated with these infections. This is also true in association with tuberculosis and other granulomatous infections at times.

DR. SHERRY: From our discussion so far, it seems that we should be most suspicious of some obscure granulomatous disease or chronic infection as the primary illness, and that the salmonella organism in this case may prove to be of more than incidental interest.

Now let us turn to some of the other interesting features. Certainly the severe hypoalbuminemia and hypoproteinemia attracted considerable attention. Dr. Davidson, would you evaluate this particular feature for us?

DR. JOHN DAVIDSON: Late in the course of this patient's illness, as judged from the protocol, results of liver function tests were deranged severely enough to explain hypoproteinemia. Early in her course, however, results of liver function studies were relatively normal at a time when hypoproteinemia was documented several times. This brings up the possibility that something other than liver disease caused the hypoproteinemia. Usually, this can be explained on the basis of protein loss as seen in nephrosis or exfoliative dermatitis, or some other more or less obvious condition. When none of these things are present to explain it, it is important to consider the possibility of protein loss into the gut. Actually, this idea was entertained in this particular patient. For that reason she was given radioactive polyvinylpyrrolidine in an attempt to see if a protein-losing gastroenteropathy was a factor in causing hypoproteinemia in her illness. Unfortunately, accurate stool collections were not obtained and therefore I did not complete the study. Protein-losing enteropathy occurs in a wide variety of illnesses. I have never seen it in a chronic granulomatous disease such as Hodgkin's or tuberculosis. There is some anatomic evidence that lymphangectasia in the small bowel villi is a common factor in many widely diverse diseases, such as regional ileitis, constrictive pericarditis, ulcerative colitis and gluten enteropathy. It is a possibility that granulomatous obstruction of the lacteals could cause a lymphangectasia with subsequent rupture of these small vessels and then a pouring of protein-rich fluid into the gastrointestinal lumen.

DR. SHERRY: If you were to give an edu-

cated guess, would you favor a protein-losing enteropathy?

DR. DAVIDSON: Yes, I would, Dr. Sherry, simply because many patients that we have studied with relatively normal liver functions, and no other obvious cause for hypoproteinemia, have turned out to have an elevated excretion of polyvinylpyrrolidine in the stool to explain the hypoproteinemia.

DR. SHERRY: At times this patient was described as having abnormal reactions to liver function tests; at one point it was probably associated with kanamycin toxicity, but there were also abnormalities which appeared late in her course. Dr. Karl, is there sufficient evidence to indicate that the liver was the site of any disease, and if so, what type?

DR. MICHAEL M. KARL: These liver function tests suggest cholestatic jaundice associated with minimal hepatocellular disease. I am not impressed that they represent a very important feature of this illness. I believe that they are a reflection of some systemic disease, possibly a bacteremia or a granulomatous process such as has been mentioned previously. They certainly are not severe enough to account for the low serum albumin on the basis of liver disease. I really believe that the liver plays a very unimportant part in this disease, except as a reflection of a severe systemic illness.

DR. SHERRY: One type of infection which we frequently overlook, particularly in older people, is bacterial endocarditis. Our patient certainly had anemia, splenomegaly and some petechiae. How seriously should we consider endocarditis in our patient?

DR. KARL: She had many clinical features to at least suggest this, but the repeatedly negative blood cultures, of course, are strong evidence against this. Salmonella endocarditis occurs occasionally and possibly should be mentioned.

DR. SHERRY: Let us consider the infections which developed toward the end of her illness; at one point she was suspected of having a subdiaphragmatic abscess, then her submaxillary gland began to suppurate, and finally a rapidly spreading pulmonary infiltrate developed which was associated with the production of large amounts of purulent sputum.

Dr. Goldman, would you agree with me that the latter findings are most suggestive of the development of a suppurative pneumonia?

DR. ALFRED GOLDMAN: I think so. I believe this occurred terminally. She had received a lot of antibiotic therapy, and probably had resistant organisms. A staphylococcus and monilia were cultured from one of the submaxillary glands. Although the question of a possible salmonella infection in the lung had been brought up, it did not play a part terminally. The effusion that she had at first on the left side apparently developed after the splenectomy and one always suspects something under the diaphragm. This does not necessarily have to be an actual abscess, since a subdiaphragmatic irritation may be enough to give a pleural reaction. Subsequently right pleural effusion developed, which was more marked than the left pleural effusion, and also bilateral pulmonary infiltrates. I think the pulmonary lesions can best be explained by a terminal suppurative pneumonia.

DR. SHERRY: There were many reasons for a diminished immunity in this patient; she became very debilitated and rapidly spreading decubiti developed. The possibility of an underlying hypogammaglobulinemia also existed. However, I was intrigued by the fact that she had been receiving prolonged, broad-spectrum antibiotic therapy, and wondered to what extent this may have contributed to the development of rapidly spreading infection with antibiotic-resistant staphylococci and fungi.

Dr. Harford, would you comment on the appearance of fungal infection in debilitated subjects maintained on broad-spectrum antibiotic therapy for long periods of time?

DR. HARFORD: It is true that the intestinal flora is altered by the oral administration of broad-spectrum antibiotics and candida can often be cultivated from the stool under these conditions. However, it is usually difficult to know whether these candida are causing any clinical manifestations. I think that the salivary gland was infected by staphylococci in this case and am inclined to agree with Dr. Goldman that the terminal pneumonia may also have been staphylococcal.

DR. SHERRY: We must terminate this discussion without a clear idea of the nature or pathogenesis of the illness; I would suggest three possible interpretations: (1) The patient did have an enteric fever with a salmonella organism which led to a certain amount of splenic hyperfunction and also contributed to the development of debility, hypoproteinemia and diminished immunity. These factors plus prolonged,

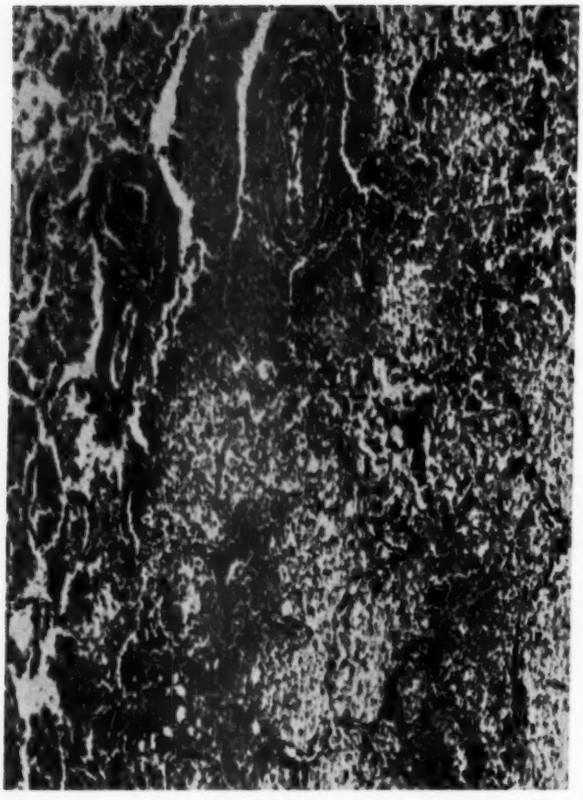


FIG. 2. Area of cryptococcal infection in lung to show empty spaces in alveoli with surrounding hemorrhage. Hematoxylin and eosin stain, original magnification × 56.

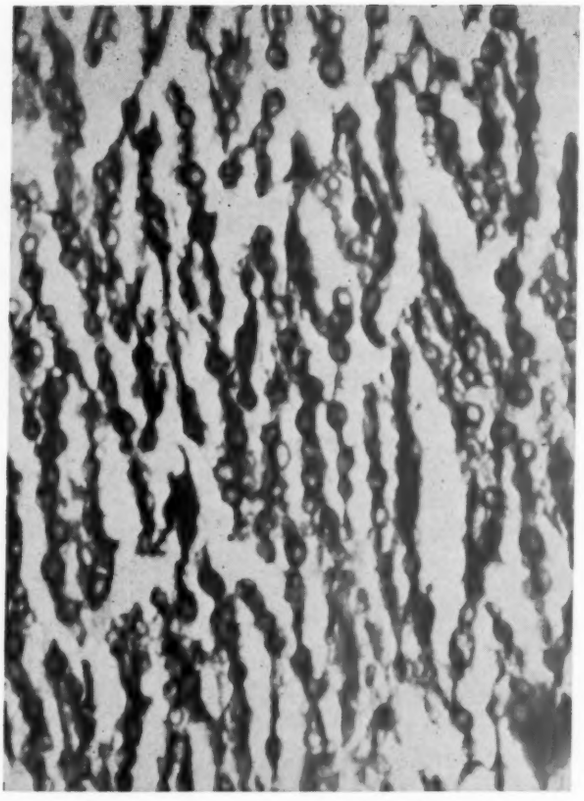


FIG. 3. Cryptococci in areas shown in Figure 1. Mucicarmine stain, original magnification × 560.

broad-spectrum antibiotic therapy resulted in a series of secondary suppurative infections (staphylococcal and perhaps fungal) which caused her death, with or without evidence of the original infection still present. (2) A much less likely possibility is that she had primary dysplenism which led to debility and diminished immunity; these factors predisposed to the salmonella infection and, following the antibiotic therapy, to a series of suppurative infections. (3) This woman had some obscure granulomatous or neoplastic disease which was not recognized during life; this caused the secondary dysplenism, debility, hypoproteinemia and diminished immunity which then resulted in a series of infections which caused her death.

PATHOLOGIC DISCUSSION

DR. ROBERT H. HEPTINSTALL: Before giving the details of this case, it would be as well to mention very briefly the main pathologic findings. These were cryptococcal infection of the left lung; acute necrotizing tracheobronchitis; collapse of both lower lobes, associated with pleural effusion of 500 cc. on each side; chronic cholecystitis and cholelithiasis; lymph node hyperplasia; fat necrosis and abscess in the tail of the pancreas; and ascites of 2,000 cc.

The causative organism, Cryptococcus neoformans, is a yeast-like non-fermenting non-myecelial non-sporulating, budding fungus with a characteristic wide capsule both in test tubes and in culture. It may affect the meninges, the skin, the lungs and other organs. In this case the lesion was confined to the lungs, and did not affect the meninges at all.

Grossly, the lobes of the left lung showed hemorrhagic nodules, particularly in the upper lobes. These hemorrhagic areas had central paler areas. The trachea and left bronchus contained large amounts of tenacious yellow mucoid material. Histologically the trachea and bronchi showed an acute and chronic inflammatory reaction. The nodules seen grossly consisted of an outer area in which hemorrhage had occurred into the alveoli. The more central areas showed a mixed picture. In places there

were large empty appearing spaces (Fig. 2) and they contained large numbers of cryptococci. (Fig. 3.) In the hematoxylin and eosin stained sections they were difficult to see appearing as small refractile spheres. In the mucicarmine stain they were shown very clearly and consisted of a small central area surrounded by a pink rim. This is because the capsule contained polysaccharide which stains intensely. The capsule was rather contracted in tissue sections and was not as wide as in direct smears or in cerebrospinal fluid taken from patients with meningitis. The cryptococci were also very clearly seen with the Gridley stain. In some areas there was a granulomatous type of reaction with the organisms present in giant cells. (Fig. 4.) Chronic inflammatory cells were also present in these areas.

The gallbladder contained some large pigment stones, but the liver itself was fairly normal, except for one small area in the right lobe with a certain degree of fibrosis. Histologically the gallbladder showed a thickened wall with infiltration by chronic inflammatory cells. The liver was normal. There was an abscess in the tail of the pancreas with adjacent fat necrosis.

There were certain enlarged lymph nodes in this case. They were confined to the abdomen, being found in the porta hepatis, and in the neighborhood of the pancreas. They were fairly big and histologically difficult to interpret. There was some blurring of the normal follicular pattern, proliferation of lymphoid cells, with some lymphoid cells in the surrounding fat. We cannot say with any certainty whether this was a lymphoma in its early stages or whether it was merely a proliferative change related to the infection in the pancreas. In favor of the latter was the localization of the affected nodes to the abdomen.

In order to anticipate the question of how long the cryptococcal infection had been present in the lung, I would say it had been there for weeks rather than months but would not like to date it any more accurately.

The *anatomic diagnoses* were: Cryptococcal infection of left lung; acute necrotizing tracheobronchitis; fat necrosis and 1 cm. abscess in tail of pancreas (Staph. aureus cultured postmortem); surgical absence of spleen; abscess formation in right submaxillary gland; chronic cholecystitis and cholelithiasis; lymph node hyperplasia; skin ulcerations; ascites 2,000 ml. and bilateral pleural effusions 500 ml. each side.

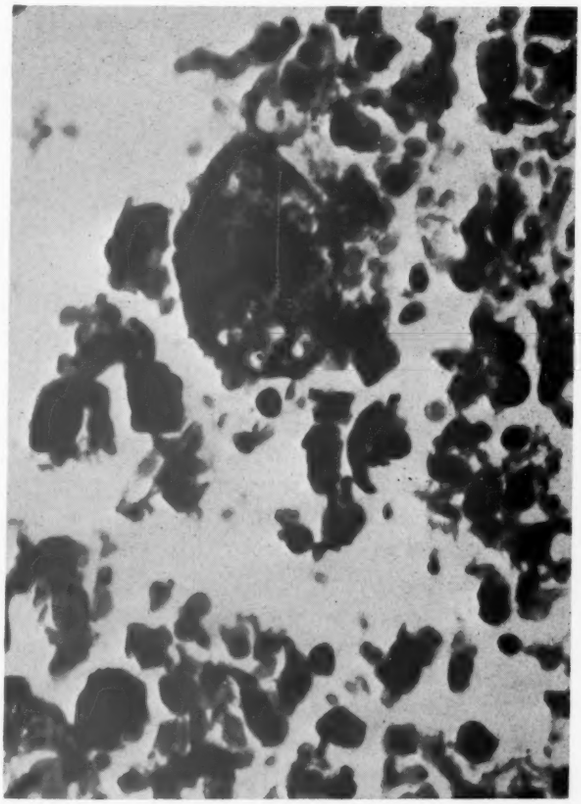


FIG. 4. Giant cell engulfing cryptococci. Hematoxylin and eosin stain, original magnification × 560.

DISCUSSION

DR. HARFORD: In view of the possibility that this patient may have been a carrier of salmonella, I should like to know whether salmonella were found in the gallbladder at autopsy. Also, did cultures of the tracheobronchial exudate show staphylococci?

DR. HEPTINSTALL: Unfortunately, culture of the gallbladder was not performed. The trachea showed a profuse growth of Proteus mirabilis, with no evidence of Staph. aureus. Staph. aureus was cultured from the abscess in the submaxillary gland, and also from the abscess in the tail of the pancreas.

DR. LOEB: Were any plasma cells noted in the inflammatory reaction?

DR. HEPTINSTALL: Plasma cells were noticed; also this lymph node is not the type of lymph node I imagine you would ordinarily see in a severe case of hypogammaglobulinemia. I have seen lymph nodes in cases of agammaglobulinemia in which they were just shells with hardly any cells at all.

Case Reports

Hodgkin's Disease of the Small Bowel*

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Less than 4 per cent of the lymphomatous disorders originate in the gastrointestinal tract [*1*], and Hodgkin's disease represents only a fraction of this group of diseases [*2*]. Of approximately 250 reported cases of primary gastrointestinal Hodgkin's disease, about fifty were located in the small bowel [*3*]. A survey of these fifty cases discloses that detailed clinical and pathologic description is available in only sixteen.

The paucity of information on this entity has prompted us to report a case and to review some of the salient aspects of small intestinal Hodgkin's disease.

CASE REPORT

A sixty-three year old Caucasian man presented with a chief complaint of five bouts of hematemesis between 2:30 A.M. and 7:00 A.M. on the day of his admission (December 23, 1959). His vomiting was heralded by moderately severe epigastric pain which awakened him from a sound sleep. The vomitus consisted primarily of bright red blood. The patient was not aware of any melena or hematochezia, nor had he ever vomited blood in the past.

In the six weeks prior to admission this man had noted progressive anorexia, a feeling of epigastric fullness early in the course of his meals, a steady, fairly-intense, mid-epigastric pain unrelieved by eating or change of position, and a 20 pound weight loss. Consultation with his private physician and radiographic study of the upper and lower gastrointestinal tract on December 10, 1959, had failed to reveal the source of the disturbance; retrospective analysis of the small intestinal views did, however, implicate some jejunal irregularities which had originally been overlooked. (Fig. 1.)

The patient's past medical history and family history were non-contributory. The patient denied fever or night sweats. He did admit that he had felt weak and tired during the recent several months. His personality traits were not suggestive of alcoholism or peptic diathesis, and he had no gastrointestinal symptoms other than those mentioned.

Initial examination revealed a blood pressure of 100/60 mm. Hg, a pulse of 90 per minute, and an oral temperature of 99.2°F. Although the patient was not in pronounced distress, his skin and conjunctivas were pale, and he appeared chronically ill. Positive findings included marked pectus excavatum, a palpable, non-tender left axillary lymph node, and a palpable, tender, ill-defined grapefruit-sized mass (approximately 12 to 15 cm. in diameter) in the medial portion of the left upper quadrant of the abdomen.

Immediate hemoglobin and hematocrit determinations were 10.5 gm. per cent and 36 volumes per cent, respectively. The white blood cell count was 12,300 per cu. mm. with 4 bands, 73 neutrophils and 21 lymphocytes. Four hours later the hemoglobin had fallen to 9.3 gm. per cent and the hematocrit to 29 volumes per cent. Administration of 2 units of whole blood raised these levels to 11 gm. per cent and 33 volumes per cent.

An emergency gastrointestinal series was inconclusive; the fluoroscopist did suspect, however, that there may have been some obstruction to the flow of barium into the third portion of the duodenum. Slight distention of the descending loop of the duodenum was noted.

Lacking a specific diagnosis, we elected to treat the patient for a possible bleeding duodenal ulcer that was not demonstrable on the roentgenogram. Although he responded fairly well to the anti-ulcer regimen, and vomited only once more (on December 25, 1959; guaiac-negative material), his hospital course was otherwise not at all encouraging. He continued to lose weight; he was weak; his epigastric distress persisted, and he had daily temperature elevations that reached 101° to 103°F. orally.

Further laboratory studies of interest included numerous hemograms with significant eosinophilia (as high as 12 per cent). Erythrocyte sedimentation rates on two occasions were within normal limits.

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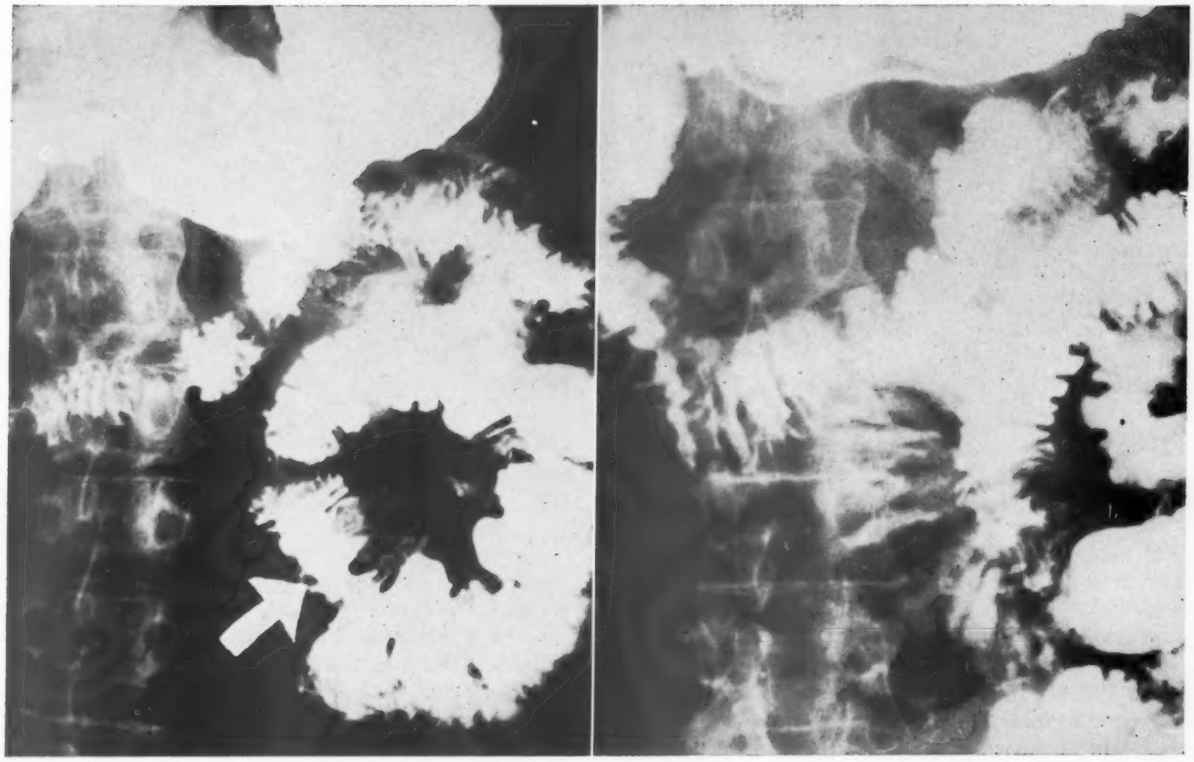


FIG. 1. Upper gastrointestinal series performed on December 10, 1959 demonstrating irregularities in jejunal pattern. (Courtesy of Dr. Carl Steckler, Richmond Hill, New York.)

C-reactive protein was 2 plus. Results of liver function studies were all within normal limits. Gastric analysis on January 7, 1960, revealed no free acid, even after histamine stimulation. The reaction to a Schilling test for vitamin B_{12} absorption was normal. Bone marrow aspiration revealed no significant abnormalities other than a relative eosinophilia. Heterophil agglutination was negative, as were the febrile agglutinin tests. Serum electrolytes were normal. Serum protein fractionation revealed a total protein of 5.2 gm. per cent with 29 per cent albumin (normal 49.7 to 70.1 per cent), 10 per cent alpha-1 globulin (normal 1.6 to 3.6 per cent), 15 per cent alpha-2 globulin (normal 4.9 to 9.1 per cent), 25 per cent beta globulin (normal 6.9 to 16.9 per cent), and 21 per cent gamma globulin (normal 7.3 to 19.7 per cent). Stool examinations were negative for ova and parasites, positive for occult blood.

Additional radiologic study, including films of the chest and of the abdomen, repeat upper gastrointestinal series, and a barium enema were not of diagnostic value. An inferior vena cavagram on January 19, 1960, demonstrated distinct elevation of the vena cava from its normal position adjacent to the spine. (Fig. 2.)

On January 21, 1960, while walking to the bathroom, the patient vomited a large amount of grossly bloody material, lost consciousness and collapsed. Subsequently he passed a copious bloody stool. Five units of whole blood were administered within the next ten hours in order to maintain his blood pressure. On the evening of that day the patient underwent a laparotomy. At operation there was no free fluid in the peritoneal cavity. The stomach and duodenum were normal. The liver was free of tumor or evidence of cirrhosis. The jejunum and ileum were marked by four areas of apparent neoplastic involvement. Three tumor sites were in the upper jejunum, one was in the

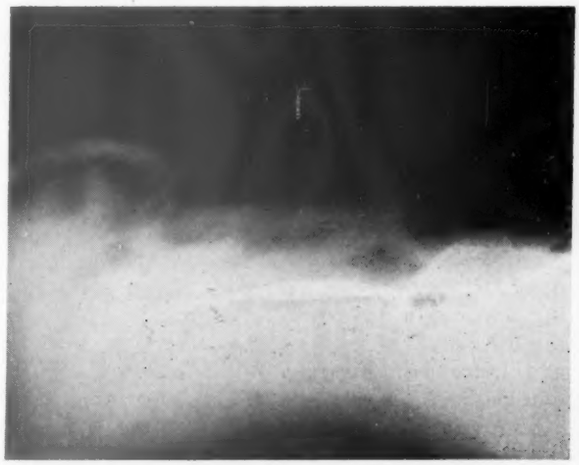


FIG. 2. Inferior vena cavagram demonstrating elevation of the vein by a retroperitoneal process.

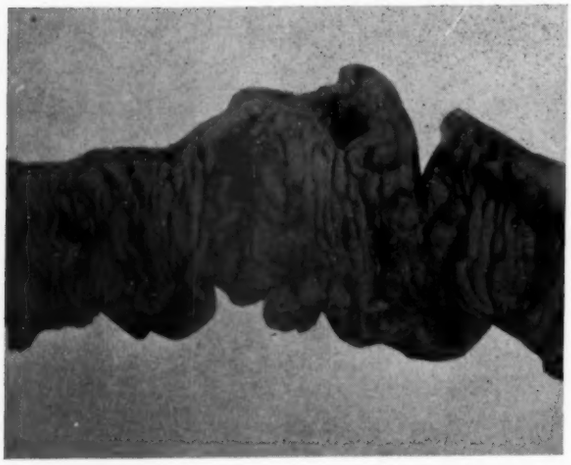


FIG. 3. Photograph of fixed gross specimen, laid open to expose ulcerative lesions.

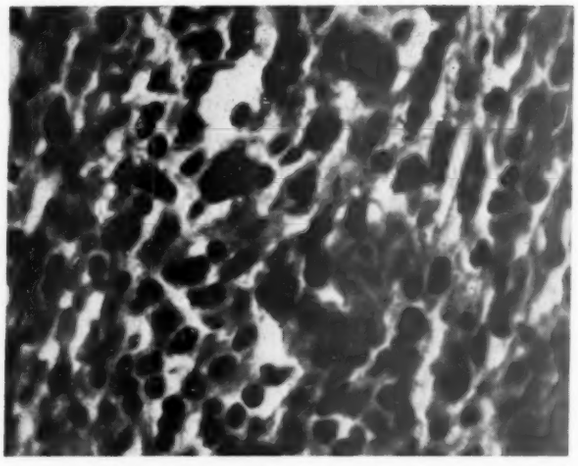


FIG. 4. Photomicrographs of the jejunal specimen. Original magnification × 430.

mid-ileum. The mesenteric and retroperitoneal lymph nodes were enlarged and firm. Approximately 4 feet of jejunum were resected, but the lesion in the mid-ileum was adherent to the dome of the bladder and to the parietal peritoneum of the left lower quadrant. Since the latter part of the small bowel did not appear to be obstructed, it was decided not to attempt to resect that part of the lesion. The final pathologic diagnosis of the lesions was Hodgkin's disease of the small bowel.

The patient's postoperative course was relatively benign. The only complicating feature was a superficial wound disruption which healed rapidly by secondary intention. The temperature curve returned to normal levels approximately one month after surgery. On February 11, 1960, a course of radiation therapy to the abdomen was begun and was continued after the patient's discharge from the hospital at the end of March. A small bowel series two months postoperatively revealed some non-specific disturbances of pattern and motility in the jejunum and ileum, but no evidence of obstruction or ulceration. When examined in the outpatient clinic three months postoperatively, the patient reported that he had been afebrile, had been eating normally and maintaining his weight, and had otherwise felt well.

The surgical specimen consisted of a 120 cm. segment of small intestine and its attached mesentery, which varied from 2 to 8 cm. in width. The serosal surface of the bowel was pinkish tan and glistening, except for several irregular areas in which moderately dense, whitish, opaque adhesions bound portions of the omentum to the bowel. The intestinal wall opposite these areas of serosal opacification was thickened and indurated. Opening of the bowel along the antimesenteric border revealed six separate mucosal ulcerations. These were circumferentially disposed. The largest ulcer was 5 cm. wide. The base of each ulcer was ragged and covered with yellowish gray, necrotic debris. (Fig. 3.) The ulcer margins were thickened and slightly undermined. In several places there was almost complete penetration of the crater through the bowel wall, but in other sites the wall was thickened, despite the apparent destruction of the mucosa and submucosa. Palpable within the mesentery were numerous moderately firm lymph nodes, the largest of which was 2.5 cm. in diameter and the cut surface of which appeared homogeneously reddish tan.

On microscopic examination the ulcerative lesions exhibited extensive destruction of the mucosa and submucosa, overlying which was necrotic cellular debris enmeshed in eosinophilic fibrinous material. The muscularis was infiltrated and almost completely replaced by a variety of cells, including small mononuclear cells, eosinophils, plasma cells and large reticulum cells. These latter cells had enlarged, dark, coarsely-vesicular nuclei with prominent nucleoli. A few distinctly neoplastic appearing cells with lobulated, hyperchromatic nuclei and the histocharacteristics of Reed-Sternberg cells were present. (Fig. 4.) The stromal elements of the remainder of the bowel wall exhibited fibrinoid necrosis and fibroblastic activity. In many areas the ulcerative process had penetrated almost entirely through the bowel wall and had apparently stimulated fibroblastic proliferation in the adjacent fatty tissue. Some of the cells had even infiltrated the peri-intestinal fat.

Sections of the enlarged lymph nodes revealed preservation of the normal architecture, but there was marked dilatation of the subcapsular sinuses. The sinuses throughout the nodes exhibited prominent littoral cells and contained a mixture of plasma cells, neutrophils, eosinophils and occasional large mononuclear cells. The lymphoid follicles were of moderate size, were increased in number and had active germinal centers.

Direct tissue smears from the primary lesions were negative for acid-fast bacilli. Tissue sections stained by the Fite and Gomori methods for tubercle bacilli

and fungi were negative. Polarized light examination of the small bowel sections failed to reveal birefringent material.

The histologic examination of the frozen sections of the intestinal lesions was not conclusive, but the fixed tissue diagnosis was Hodgkin's disease of the small intestine. The lymph node changes were interpreted as representing reactive hyperplasia.

COMMENTS

Detailed and well documented descriptions of this condition are far from abundant in the medical literature; nevertheless, combining the data from the reported cases with our own experience does permit us to point out some general observations about Hodgkin's disease of the small intestine.

Grossly, Hodgkin's disease of the small bowel seems to produce surprisingly little serosal reaction in the presence of extensive destructive changes in the mucosa and submucosa. The areas of ulceration tend to be oriented in the transverse axis, frequently with circumferential involvement. The bowel wall may be markedly thickened and almost totally infiltrated with neoplastic cells. Histologically, Hodgkin's disease of the small bowel manifests the same variability in the degree of fibrosis, cellularity, eosinophilia and number of bizarre reticulum cells as does Hodgkin's disease of other organs. The specimen from our patient, for instance, contained relatively few Reed-Sternberg cells but had many distinctly neoplastic-appearing reticulum cells.

Of particular interest is the regularly reported mesenteric lymphadenopathy, such as was seen in our case. Only rarely do these lymph nodes exhibit the same neoplastic process as is found in the bowel lesions; rather, they show chronic follicular lymphadenitis of a non-specific type, as might be expected in nodes draining any area of extensive ulceration and its attendant secondary infection. In this connection it would seem that Hodgkin's disease of the small intestine differs somewhat from Hodgkin's disease of other parts of the gastrointestinal tract in that it is less likely to be associated with a generalized form of the disease [*4–9*]. Further elucidation of this and other pathologic features of Hodgkin's disease of the small bowel must await future reports of similar cases.

Review of the clinical aspects of the published reports of this disorder indicates that the average patient first reports symptoms in the fifth decade of life, but the range of the age of onset is from thirty-six to sixty-nine years. Although gastrointestinal lymphomas generally are more common in men, Hodgkin's disease of the small intestine is more evenly distributed between the sexes [*10*]. The location of these tumors in the small bowel was reviewed by Portmann in his analysis of forty-five cases found in the literature between 1913 and 1955 [*3*]. He found that 12.5 per cent of the lesions were in the duodenum, 55 per cent were in the jejunum or proximal ileum, 20 per cent were in the terminal ileum and 12.5 per cent involved the entire small bowel. Our survey of the literature impresses us with the fact that the lesions are more often multiple than single and that they occur at random throughout the small intestine, as in the case described herein.

The diagnosis of this condition is rarely made clinically and usually awaits surgical or postmortem discovery. With the exception of nonspecific constitutional features, such as fever, malaise and weight loss, the symptoms are those of the late complications of the disease. These may include abdominal pain and distention, vomiting, hematemesis, melena, diarrhea, a sprue-like syndrome and even intestinal perforation and subsequent peritonitis. Unless bleeding is a prominent occurrence, anemia is uncommon early in the disease. Examination may reveal a palpable abdominal mass, as it did in our patient [*10–16*].

Laboratory findings, although not in themselves diagnostic, sometimes implicate the lymphoma group, notably Hodgkin's disease, as the source of the suspected gastrointestinal lesions. As in Hodgkin's disease of other organs, a significant eosinophilia may be noted, as in our patient. The elevation of the serum C-reactive protein is also thought to be more prominent in the lymphomas than in other neoplasms. Hypoalbuminemia and relative elevation of the various globulin fractions has also been a nonspecific feature of Hodgkin's disease, even when there is no apparent hepatic involvement.

Radiographic studies may suggest the diagnosis, particularly if a small bowel series demonstrates multiple ulcerating lesions separated by strips of normal mucosa and associated with alternating dilatation and narrowing of the bowel lumen [*17*]. Enlarged retroperitoneal lymph nodes, as demonstrated by an inferior vena cavagram in our patient, may be of further value in diagnosis.

Treatment of Hodgkin's disease of the small bowel consists of surgical resection and postoperative radiotherapy. Nitrogen mustard has been reported to be of some palliative value in those patients with recurrent or residual disease [*18*]. Steroids have not been found to be significantly beneficial [*19*]. Of the reported cases, more than 50 per cent of the patients have died before or immediately after surgery. The patients with solitary lesions and no demonstrable lymphatic metastases who have survived surgery are expected to have the more auspicious prognosis; yet, even in this relatively favorable group, the longest recorded survival after surgery is two years [*4*]. This, it would appear that small intestinal Hodgkin's disease fits the statement of Hall and Olson, " . . . there is no evidence . . . to suggest that localized Hodgkin's disease is curable" [*18*].

SUMMARY

A case of small intestinal Hodgkin's disease in a sixty-three year old man is presented. The pathologic and clinical features of this condition, as reviewed in the medical literature and as observed in our case, are discussed.

Acknowledgement: We are indebted to Captain R. Volk, (MC), USN, Chief of Medicine, for helpful suggestions and constructive criticism.

ADDENDUM

During the fourth postoperative month the patient's condition began to deteriorate. He had severe, intermittent, cramping abdominal pain and frequently vomited after meals. On July 25, 1960, six months after surgery and four months after the completion of the course of radiotherapy, the patient was readmitted to the hospital. He weighed 110 pounds, which was 20 pounds less than he had weighed at the time of his discharge, and 50 pounds less than he had weighed in December, 1959. His admission had been engendered by a one-week period of unrelenting vomiting attacks and inability to retain even liquid nutrients.

Gastrointestinal x-ray study revealed an area of pronounced duodenal narrowing just proximal to the site of the previous anastomosis. An inferior vena cavagram demonstrated a diminution in the size of the previously enlarged retroperitoneal nodes.

Exploratory laparotomy on July 28, 1960, disclosed a firm, intrinsic tumor mass in the second portion of the duodenum. Other intramural lesions were palpable in the upper jejunum. There was no gross evidence of peritoneal implants or involvement of the liver and spleen. A palliative bypass was achieved by anastomosing a loop of proximal jejunum to the fundus of the gallbladder and then performing a gastrojejunostomy on the same loop of bowel.

On the third postoperative day the patient's nasogastric tube was removed, his bowel sounds were hypoactive but present, and he had passed flatus. Later that day he became disoriented, lapsed into semicoma, and was found to have bilateral Babinski signs and fixed, miotic pupils. With intensive nursing care the patient managed to survive for another week. A brainstem hemorrhage was thought to have explained the terminal events.

Significant postmortem findings included 300 cc. of serosanguinous fluid in the abdominal cavity, thickening and opacification of the peritoneum, and dense adhesions binding many loops of small bowel together and to the urinary bladder. The cholecystojejunostomy and the gastrojejunostomy sites were intact. Two small bowel fistulas were found. One of these led to a right-sided retroperitoneal abscess that contained approximately 200 cc. of grayish yellow pus.

Ulcerating neoplastic lesions were found in the stomach, the duodenum, the jejunum, the ileum, the cecum and the ascending and transverse colon. The tumors were oriented in the transverse axis of the bowel. Several of the lesions in the small bowel were completely circumferential. All the ulcers were similar in that they had rolled and elevated margins with yellowish gray necrotic bases and induration of the subjacent bowel wall. There were many firm mesenteric lymph nodes that measured up to 1 cm. in diameter. Two large lymph nodes measuring 3 cm. in diameter were located in the para-aortic chain just cephalad to the renal arteries.

A well circumscribed, spheroidal lesion, measuring 2.5 cm. in diameter, was discovered in the left anterior frontal area at the level of the superior and middle frontal gyri. This lesion extended from the level of the superior frontal gyrus to the third ventricle. It was softened and hemorrhagic. There was evidence of increased intracranial pressure. The brain weighed 1,470 gm.

The histologic appearance of the ulcerative

lesions in the gastrointestinal tract was similar in all respects to that described in the original surgical specimen. The para-aortic lymph nodes, as well as most of the lymph nodes of the mesentery, exhibited a combination of radiation effects and involvement with Hodgkin's disease. In some of the lymph nodes radiation had not completely destroyed the usual architectural features, and typical Reed-Sternberg cells were located readily. One small tumor nodule was found in the wall of the left ventricle. The cells in this nodule were loosely arranged and were accompanied by considerable necrosis, edema and congestion of the adjacent myocardial tissue. The cerebral lesion was also neoplastic. The secondary hemorrhage found in this lesion was considered to be the immediate cause of death.

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Angiographic and Hemodynamic Studies of a Postlaminectomy Iliac Arterial Inferior Vena Caval Fistula*

Cure by Incision and Suture of the Lesion

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ONE hundred and thirteen instances of vascular injury during surgical treatment of herniated intervertebral disc have been reported in the literature [*1–13*]. In eleven of these patients the injury led to the development of a fistula between the inferior vena cava and adjacent arterial structures, with serious cardiovascular consequences [*1,2,5–13*].

Reported herein is another case of arterial caval fistula following laminectomy. It is unique in that the abnormal communication was visualized by intravenous abdominal aortography [*14*]. Hemodynamic studies provided data regarding the rate of blood flow through the fistula and delineated the accompanying severe disturbances in cardiac function. Subsequently the communication was closed at operation and six months later repeat aortography revealed that the shunt had been obliterated successfully.

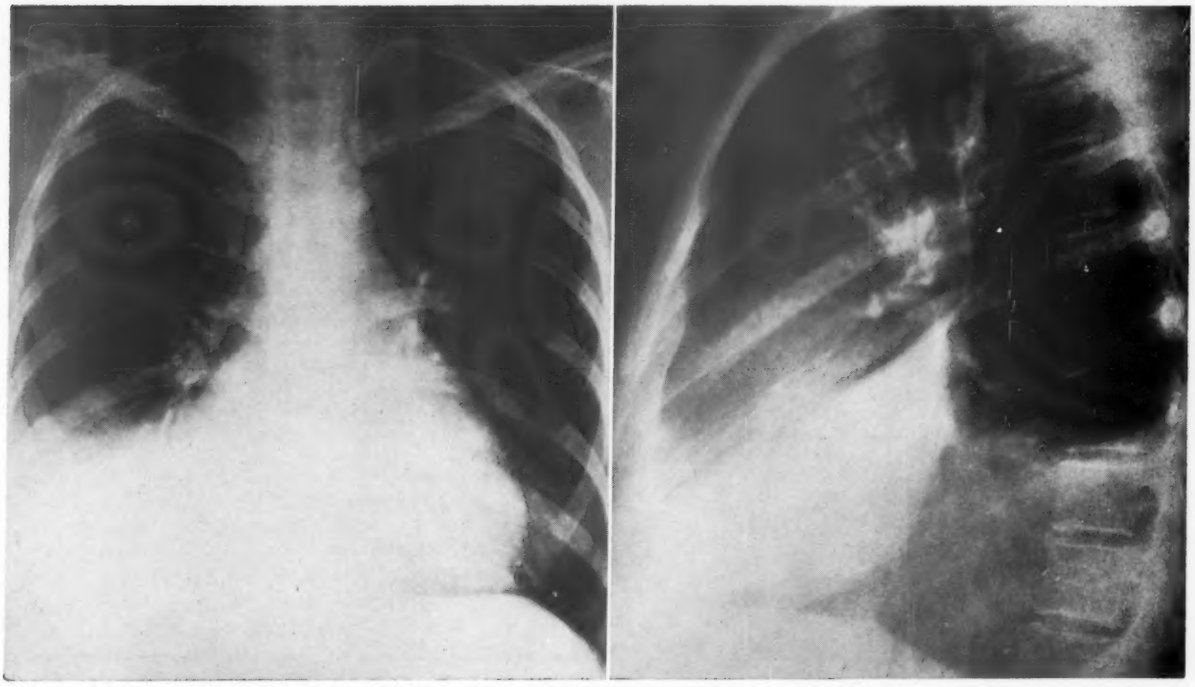
CASE REPORT

A forty-six year old white woman (New York Hospital No. 823,251) was admitted on May 6, 1959 with complaints of dyspnea, abdominal distention and weakness. Laminectomy for removal of a herniated nucleus pulposus between the fourth and fifth lumbar vertebra that had caused severe pain in the lower part of the back was performed at another hospital nine months prior to admission. Soon after the operation persistent epigastric pain, nausea and vomiting developed and were unrelieved by antacids. Severe weakness and distention of the abdomen followed. Two months after operation the patient was admitted to a hospital where anemia was discovered, and iron and a low salt diet was prescribed. Two months later, after edema of the feet developed, mercurial diuretics were given but only with transient relief. In the ensuing month, despite the administration of digitalis and mercurial diuretics, dyspnea, edema of the extremities and trunk, ascites and gastrointestinal distress increased, causing the patient to become bedridden. The patient had been well in the past except for a thyroidectomy in 1945 because of tracheal compression. In 1957 she had had an appendectomy without complications. Two children, aged twenty-three and eighteen, were alive and well.

Physical examination disclosed a well developed woman who showed signs of recent weight loss and required two pillows because of orthopnea. Her weight was 61.4 kg. The blood pressure was 118/50 mm. Hg in the arms and 115/60 in the legs. The heart was enlarged. The rhythm was regular at 70 per minute. A systolic murmur was heard all over the precordium. The second sound was closely split without accentuation. A loud, harsh continuous bruit was heard all over the thorax and abdomen, extending down as far as the popliteal spaces and loudest over the right groin. The respiratory rate was 18 per minute. There were dullness and diminished breath sounds at the right base; there were no rales. The abdomen was distended; dullness in both flanks and a fluid wave was elicited. No abdominal masses were felt. Three plus pitting edema of the extremities extended to the level of the mid-thighs. The pelvic and rectal examinations were within normal limits.

Laboratory data revealed the following: hemoglobin, 14.8 gm./100 ml.; erythrocyte count, 5.3 million/cu. mm.; leukocytes, 7,800/cu. mm.; and hematocrit, 47 per cent. The differential count was

* From the Departments of Radiology, Surgery and Medicine and the Cardiopulmonary Laboratory of The New York Hospital-Cornell Medical Center, New York. Aided by a grant from the U. S. Public Health Institute (No. H-3918), American Heart Association and New York Heart Association. Manuscript received May 16, 1960.



1A 1B

FIG. 1. Teleroentgenograms showing cardiac enlargement and right pleural effusion, in a forty-six year old woman, nine months after herniated disc operation. A, frontal x-ray film. B, lateral view.

normal. The erythrocyte sedimentation rate was 11 mm. (Wintrobe). Blood chemistry studies gave the following results: urea, 13 mg. per cent; acid phosphatase, 3.7 Gutman units; alkaline phosphatase, 4.7 Bodansky units; bilirubin, total 0.8; direct, 0.3 and indirect, 0.5 mg. per cent; cholesterol, 152 mg. per cent; total proteins, 4.6 gm. per cent, with albumin 2.7 and globulin 1.9 gm.; and glutamic-oxalacetic transaminase, 50 units/ml. The urine was normal. Electrocardiograms showed a rate of 72, regular sinus rhythm; no deviation of the electrical axis, P-R interval 0.18 second; QRS interval, 0.08 second; and alterations of the T waves due to digitalis. Roentgenograms of the thorax (Fig. 1) showed enlargement of the heart and a large right pleural effusion. The venous pressure was 160 mm. water, rising with hepatic pressure to 280 mm. The circulation time (Decholin®) was twenty seconds. Abdominal paracentesis yielded 2,100 cc. yellow fluid which contained erythrocytes, 3,090/cu. mm.; leukocytes, 350/cu. mm. with differential count of 86 mononuclear and 14 polynuclear cells. Cytologic studies of the ascitic fluid did not reveal malignant cells.

Following the abdominal paracentesis, a smooth, non-tender liver was palpated five fingerbreadths below the costal margin. A 5 cm. ill defined mass with a systolic thrill was also felt in the right lower quadrant of the abdomen.

Cardiac catheterization performed on May 10, 1959, revealed venous hypertension in both the pulmonary and systemic circuits due to increased

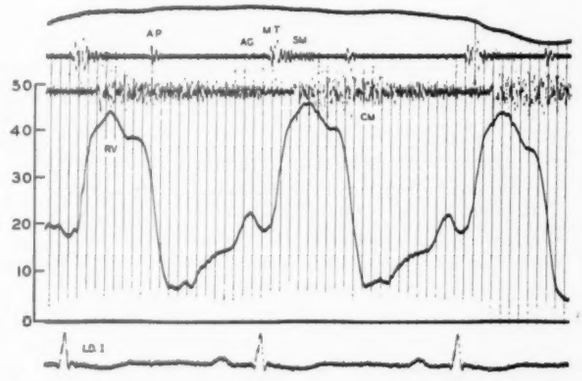


FIG. 2. Simultaneously recorded pneumotachogram, phonocardiograms, right ventricular pressure and electrocardiographic lead I (reading from top to bottom). Record speed 100 mm./second; time lines, .04 second. Pressure calibration in mm. Hg. Note end diastolic pressure in right ventricle (RV) preceded by a wave due to prominent atrial systole. Upper phonocardiogram, recorded from fourth intercostal space between apex and left sternal edge, demonstrates split second sound with pulmonic component (P) following aortic component (A) by .02 second, a low intensity gallop sound (AG) at time of atrial contraction, loud tricuspid closure sound (T) following mitral closure (M), and a short early systolic murmur (SM). Lower phonocardiogram, recorded over abdominal aorta below and left of umbilicus, shows the continuous murmur (CM), the systolic component of which starts well after the onset of cardiac systole and is preceded by a sharp, loud sound. In pneumotachogram expiration is up; inspiration is down.

TABLE I

DATA DERIVED FROM CARDIAC CATHETERIZATION

Site	Blood O_2 Content (vol. %)	Pressures (mm. Hg) Systolic/Diastolic	Mean
Brachial artery (O_2Hgb. % saturation)	18.0 (97.5%)	122/46	89
Pulmonary "capillary"	...	...	19
Pulmonary artery	14.8	43/16	28
Right ventricle	14.9	43/19	...
Right atrium	15.1	...	12
Superior vena cava	11.1	...	...
Inferior vena cava	16.1	...	...
Oxygen consumption	179 ml./min.	108 ml./min./M^2	
Cardiac output (Fick)	5.96 L./min.	3.61 L./min./M^2	
Cardiac output (dye)	5.94 L./min.	3.60 L./min./M^2	
Fistula flow (dye)	3.55 L./min.	2.15 L./min./M^2	
Cardiac rate	72	...	
Pulmonary vascular resistance	120 dynes sec. cm.$^{-5}$	...	
Systemic vascular resistance			
(including fistula)	1,030 dynes sec. cm.$^{-5}$	...	
(excluding fistula)	2,550 dynes sec. cm.$^{-5}$	...	

filling pressure of both ventricles. (Table I and Fig. 2.) The brachial arterial pulse pressure was 76 mm. Hg and the diastolic pressure was low. (Fig. 3.) The cardiac output was in the high normal range. The arteriovenous blood oxygen difference was narrow. Blood from the inferior vena cava contained 5 volumes per cent more oxygen than superior vena caval blood and had an oxyhemoglobin saturation of 88 per cent. This suggested a left-right shunt into the inferior vena cava. By application of a simple mixing formula to these oxygen data, it could be calculated that 76 per cent of inflow into the pulmonary artery was derived from the inferior vena cava.

Indocyanine green was injected into the pulmonary artery and dye dilution curves were recorded (with a cuvette) from the brachial artery and from the inferior vena cava via a second catheter previously positioned in this vessel. (Fig. 4.) These curves confirmed the presence of an arterial-caval shunt. From these curves and knowing the fraction of cardiac output flowing through the inferior vena cava, the shunt was calculated to be 3.55 L. per minute or 60 per cent of the cardiac output.* Blood flow to the tissues was therefore markedly restricted, to 1.46 L./minute/M^2. From the orifice formula, it was deduced that the fistula was only 4 mm. in diameter. Systemic vascular resistance as conventionally calculated was normal; however, when the fistula flow was excluded, the resistance of the vascular bed was over twice normal. Intravenous abdominal aortography revealed an aortico-inferior vena caval shunt. (Fig. 5.)

On May 20, 1959, operation via a midline xiphoid to pubic incision was followed by evacuation of about 3,000 cc. fluid from the abdomen. There was moderate enlargement of the liver and the intestines were edematous. The patient was placed in a slight Trendelenburg position, displacing the free pelvic viscera which were then walled off. A mass at the lower end of the aorta and inferior vena cava was visualized. A thrill over the right iliac artery 4 cm. below the aortic bifurcation extending into the inferior portion of the inferior vena cava was felt. When the thrill was obliterated by compression with the fingers, the systolic blood pressure rose 40 mm. Hg. The fistula between the right iliac artery and vena cava was found to be small (about 6 mm.) in diameter. Following isolation of the artery and veins starting well

* The dye curves were replotted on semi-logarithmic paper and the down slope of the initial peak of each was extrapolated. The following formula was employed to find the proportion of inferior vena caval flow (QIVC) derived from the shunt (QLR):

$$\frac{Q_{LR}}{Q_{IVC}} = \frac{\int_0^\infty C_{IVC}dt}{\int_0^\infty C_{BA}dt},$$

where $\int_0^\infty C_{IVC}dt$ and $\int_0^\infty C_{BA}dt$ are the respective areas of the extrapolated peaks in the inferior vena caval and brachial arterial curves. QLR/QIVC was found to equal 79 per cent. Since, on the basis of rate of oxygen inflow into the right heart, QIVC was 4.51 L./minute then QLR equals 3.55 L./minute. An independent estimate of QLR was made from the oxygen data by assuming that inferior vena caval blood oxygen content in the absence of a shunt would have been a normal 1 volume per cent higher than oxygen content of superior caval blood. QLR derived in this way was 3.19 L./minute and in fairly close agreement with the dye estimate.

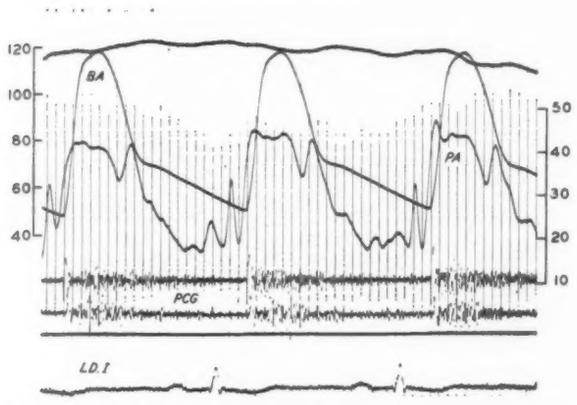


FIG. 3. Simultaneously recorded pneumotachogram, brachial arterial (BA) and pulmonary arterial (PA) pressures, phonocardiograms and electrocardiographic lead I. Record speed, 100 mm./second; time lines, .04 second. Calibrations (left for BA, right for PA) in mm. Hg. Note large pulse pressure and low diastolic pressure in BA. Increase in pulmonary arterial pressure is mainly due to elevated pulmonary venous pressure. The continuous murmur is seen in phonocardiograms recorded over lower abdominal aorta (upper) and right femoral artery (lower). The murmur is loudest during peak BA systole and diminishes during diastole. The loud sound at onset of systole is evident at both sites but occurs .015 second later in the femoral artery.

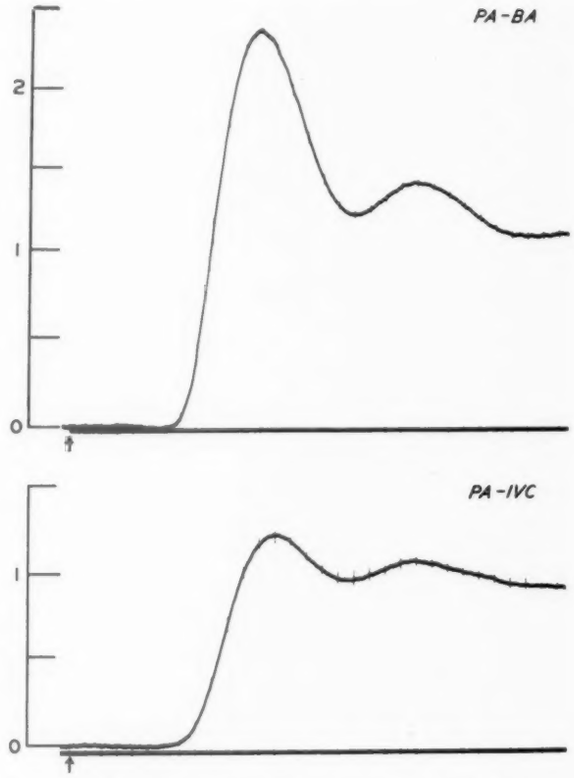


FIG. 4. Original indicator-dilution curves recorded from brachial artery (BA) and inferior vena cava (IVC) following injection of 2.26 ml. of 0.5 per cent indocyanine green into the pulmonary artery (PA). Calibrations in milliliter of dye solution per L. of whole blood. Record speed, 5 mm./second; time lines, 1 second. Arrows indicate time of injection of dye (corrected for transit delay in needle-cuvette and catheter-cuvette systems). In BA curve, first peak represents normal initial circulation of dye. The second peak is too early and too high for normal systemic recirculation; it is due to early recirculation through the fistula. In IVC curve, rapid transit of dye through the fistula is responsible for the premature first peak, which is almost synchronous with initial circulation in BA. The second peak is due to dye that has traversed the normal vascular pathway. The curves were used in quantifying flow through the fistula (see text).

above the communication, the inferior vena cava was found to be three times its usual size. (Fig. 6.) A clamp was then placed on the inferior vena cava, the fistula incised and the inferior vena cava sutured with No. 0000 silk. Next, the right iliac artery was closed and oversewn with a bit of fistulous tract. Following this, the blood pressure was 150/80 mm. Hg; whereas, at the beginning of the operation it was 112/52 mm. Hg. The pulse slowed from 76 to 68. Good arterial pulsation distal to the site of the sutured vessels was evident. Further protection to the suture line along the iliac artery was obtained by making a cuff of some excised posterior rectus fascia and securing it by four interrupted sutures to the wall of the artery. A pad of gel foam was also placed about the right iliac artery. Following operation the patient improved remarkably. Diuresis occurred, with an 8 kg. weight loss. Her dyspnea disappeared and she soon became ambulatory and well. The blood pressure was 120/80 mm. Hg. The roentgenogram of the chest (Fig. 7) showed clear lung fields and a normal heart.

Subsequent examinations found the patient to be entirely well except for severe pain over the left side of the back radiating down the left leg. On January 8, 1960, the patient was readmitted to The New York Hospital for evaluation of the back pain. The heart was normal in size and without murmurs; the blood pressure was 124/64 mm. Hg. A soft systolic murmur was heard in the abdomen. Her weight was 61 kg. and there was no dyspnea, ankle edema or ascites. Intravenous abdominal aortography showed a normal abdominal aorta. (Fig. 8.) Myelographic roentgen studies were within normal limits. On January 29, 1960 re-exploration of the intervertebral space between the fourth and fifth lumbar vertebra failed to show retained disc fragments or nerve compression. The back pain and sciatica syndrome was not alleviated.

COMMENTS

Arteriovenous fistula following lumbar laminectomy for removal of a herniated disc was described first by Linton and White [5] in 1945. Resection of the fistula and repair of the vessels subsequently led to cure of the patient. The next



FIG. 5A. Intravenous frontal abdominal aortogram showing the aorticocaval shunt.

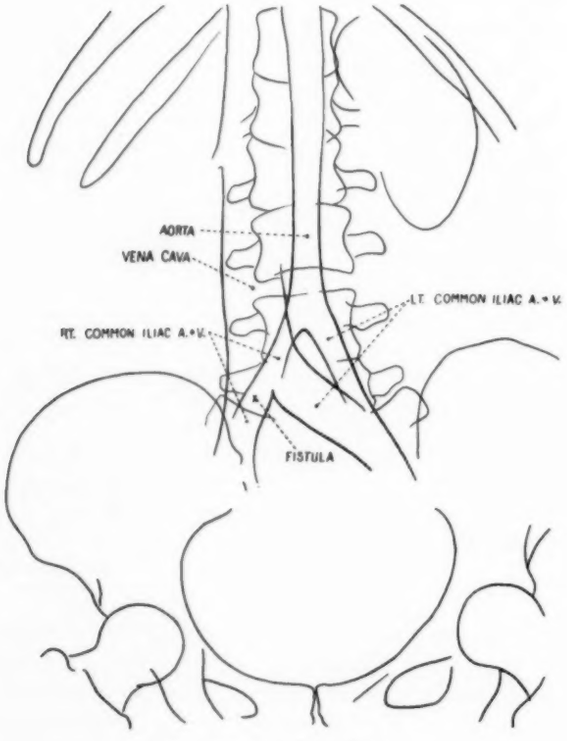


FIG. 5B. Tracing of 5A.

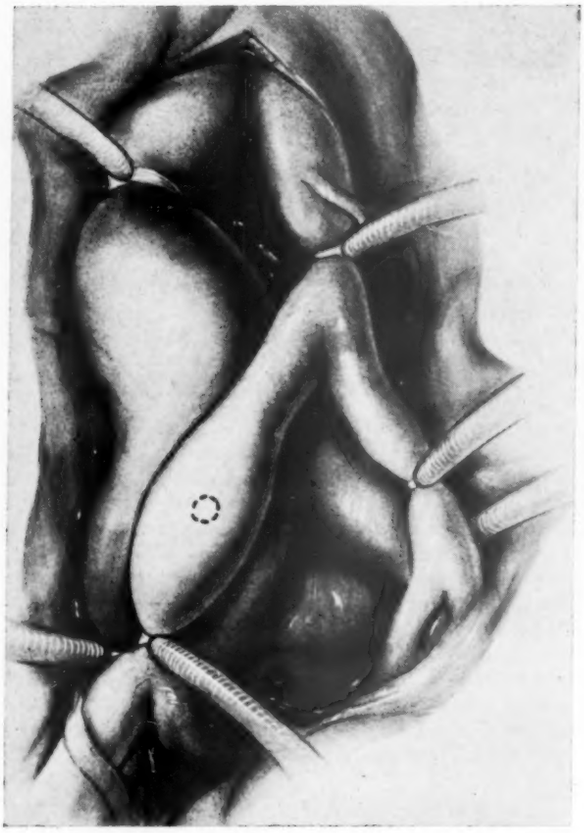


FIG. 6A. Diagramatic sketch of operative findings. The aorta and inferior vena cava above and below the fistula isolated by tapes. The small broken-lined circle represents the arteriovenous fistula.

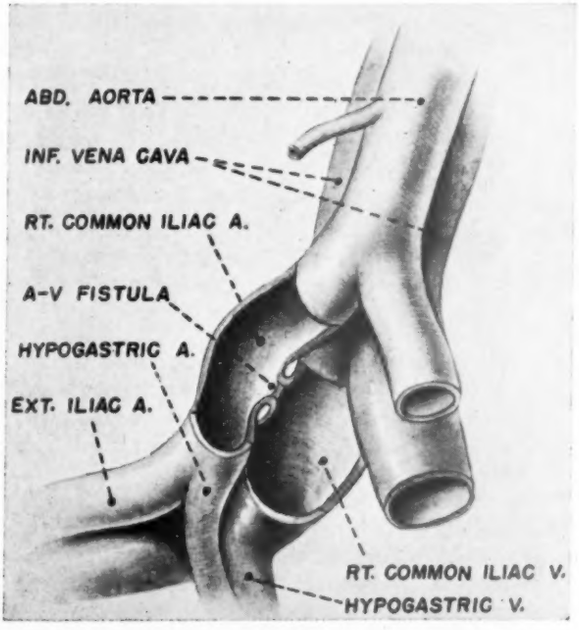


FIG. 6B. Diagramatic sketch of detailed anatomic features of the fistula.



FIG. 7. The normal (postoperative) frontal teleroentgenogram.



FIG. 8. The intravenous abdominal aortogram made six months after cure of aorticoinferior vena caval fistula.

case was reported by Holscher [*6*], who revealed that while supervising an able surgeon in the removal of a herniated disc (indeed, he was describing Linton and White's case), a depth sounding with a closed pituitary rongeur for the anterior portion of the annular ligament was followed by a copious gush of blood [*1*]. Nine additional instances of this lesion have been reported [*1,7,11–13*].

The most recent survey of vascular injuries following disc surgery was made by De Saussure [*4*] after polling neurosurgeons and orthopedic surgeons. One hundred and eight vascular accidents were recorded. Adding the recently reported arteriovenous fistulas [*11–13*], the total number of vascular injuries reported in the literature is 113. De Saussure also found that the pituitary rongeur was the most commonly used instrument when the injury to the blood vessel occurred. There appears to be general agreement that while too vigorous instrumentation may damage blood vessels lying immediately anterior to a disc, the strength, thickness and intactness of the anterior longitudinal ligaments and annulus fibrosis are important. Indeed, vascular injuries have occurred in most competent hands and often at a time when the disc surgery was performed with care and gentleness. Improper support of the bony skeleton in the prone position during operation is also believed to be a factor in forcing vessels against the vertebral bodies [*1*]. When the longitudinal ligament is thin and defective and there is degeneration of the annulus it is easy to understand how such vessels may even protrude into the intervertebral space and be accidentally damaged by instruments. Indeed, in two instances gut, and in another, ureteral tissues have been recovered from the pituitary forceps [*1,4*].

The diagnosis of vascular injury during disc surgery is difficult and usually not obvious. In less than half of the cases collected by De Saussure [*4*] and Harbison [*1*] there was profuse bleeding through the interspace. Precipitous drop in blood pressure and a shock state were important signs of internal hemorrhage. An abdominal mass, increasing in size, and a bruit over the abdomen were significant signs. In the patients with arteriovenous fistulas, the characteristic machinery murmur and progressive intractable heart failure, as in our case, eventu-

ally led to the diagnosis. Successful treatment of vascular injuries associated with disc surgery requires prompt action to control shock and hemorrhage. Delay in exploration for the site of hemorrhage and emergency repair of the vascular injury has resulted in a high mortality [*4*].

Clinically and hemodynamically our patient, as well as those reported on in the literature [*1,5–7,11*], exhibited almost all the features that Ferguson and co-workers [*15*] observed in dogs with surgically created aortic-inferior vena caval shunts. Of twenty-five dogs with slits between the aorta and inferior vena cava measuring 7.5 to 15 mm. (average 11 mm.) in length, eleven died within forty-eight hours of acute circulatory failure, or within four to eight weeks. Ascites (which occurred three to six weeks after operation), edema of the hind legs and pulmonary edema were common among the survivors. Three animals were followed up for fifteen to eighteen months, respectively, and required supportive measures such as paracentesis, mercurial diuretics, horsemeat diet, and small transfusions. Despite these, the animals lost weight, had marked wasting of tissue and anemia. On the other hand, two animals with bilateral iliac fistulas and two with iliac-femoral shunts remained healthy for two years (despite heavy exercise and excessive salt diets) and showed none of the signs of circulatory strain exhibited by the group with central fistulas.

Careful hemodynamic studies (but without shunt flow measurements) showed that the dogs with aortic-caval fistula responded to saline and blood infusions by marked additional increase in already elevated ventricular filling pressures and cardiac outputs. Some dogs, however, responded to this added stress by a decrease in cardiac output. In a later study, twelve dogs with chronic aortic-inferior vena caval fistulas and clinical and hemodynamic failure were not improved clinically or hemodynamically by intravenous administration of lanatoside C or maintenance on digoxin [*16*].

Cardiac performance in our patient was severely impaired. Although cardiac output was normal, it was lower than usual for an arteriovenous fistula. Blood flow to the tissues was markedly curtailed, constituting only 40 per cent of the output. It is significant that the patient was fully digitalized when the hemodynamic data were obtained. It is conceivable that coexisting intrinsic heart disease modified the response to a peripheral arteriovenous shunt. However, evidence of heart disease postoperatively was lacking. It is more probable that initially the cardiac output was much increased and that this acute load led to progressive deterioration of cardiac function, subsequent decline in output, and inability to maintain a normal blood flow to the tissues in the presence of the shunt.

SUMMARY

An arteriovenous fistula between the right iliac artery and inferior vena cava produced accidentally at laminectomy for a herniated disc in a forty-six year old woman resulted in marked progressive cardiac failure which was refractory to conventional treatment. The lesion was recognized by its classic manifestations nine months after it was produced. Intravenous abdominal aortography provided a preoperative view of the aorticovena caval fistula. Cardiac catheterization revealed advanced hemodynamic derangements and demonstrated that 60 per cent of the cardiac output flowed through the fistula. As in the previously reported cases, excision of the fistula and restoration of the blood vessel lumina produced a dramatic cure.

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The Association of Polycythemia with a Cerebellar Hemangioblastoma*

The Production of an Erythropoiesis Stimulating Factor by the Tumor

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POLYCYTHEMIA has been reported in association with various neoplasms [*1–6*]. However, it is only with renal [*7–23*] and cerebellar tumors [*24–40*] that there have been a sufficient number of cases to establish the significance of this association.

In 1943 Carpenter et al. [*25*] reported two patients with cerebellar hemangioblastomas with associated polycythemia. Since this report forty such patients have been noted [*24–40*]. Hematologically the patients have shown an erythrocytosis with no associated splenomegaly, or increase in the white cell or platelet count that might suggest a chance association of the tumors and polycythemia vera. In twenty-one cases the elevated red cell indices returned to normal following resection of the tumor [*25–27, 29,34–37,39,40*]. It is the purpose of this report to add an additional patient with associated polycythemia and cerebellar hemangioblastoma and to present our studies directed toward understanding this association.

CASE HISTORY

The patient, a thirty-nine year old salesman known to have a recurrent cerebellar hemangioblastoma, was admitted to the Metabolism Service of the National Cancer Institute on March 18, 1958 for hematologic studies. The patient was well until 1936 when (at eighteen years of age) he noted headaches, nausea, vomiting, blurring of vision and difficulty in walking. An exploration of the posterior cranial fossa revealed three cysts in the left cerebellar hemisphere. These cysts were resected and were shown on histological examination to be cerebellar hemangioblastomas. During the ensuing thirteen years the patient noted significant improvement of all symptoms, with only minimal ataxia as a residual.

In 1949 a blind spot in the lower field of vision in the right eye developed. A hemangioma of the right retina was discovered and removed by electrocoagulation. Four months following this procedure he had a recurrence of severe nausea, vomiting and difficulty with balance. The posterior fossa was explored and cerebellar hemangioblastomas of the right and left cerebellar hemispheres were removed. The hemoglobin prior to surgery was 18 gm. per cent; the red count was 6.1 million per cu. mm. One week following the procedure the hemoglobin was 13.5, at three weeks the hemoglobin was 12 gm. per cent. During the subsequent seven years the patient was troubled with unsteady gait and weakness but was free of other neurological symptoms. The patient was first seen at the National Institutes of Health on May 5, 1956, complaining of progressive occipital headaches, unsteadiness of gait of six months' duration, and nausea, vomiting, blurring of vision, occasional diplopia and slurring of speech for the two weeks prior to admission.

Past history and review of symptoms were noncontributory. Specifically there were no symptoms suggesting cardiac, pulmonary, or renal disease. The patient's mother died of a spinal tumor of unknown histology. The patient's father died of a "stroke" at fifty-four years of age. There were no siblings and no relatives other than the mother with symptoms suggesting von Hippel-Lindau's disease.

Pertinent positive physical findings on this admission were an inferior nasal quadrantic field defect in the right eye, nystagmus on lateral gaze and incoordination of movement most marked on the left. A brain scan twenty-four hours following the intravenous administration of I^{131} albumin and a vertebral arteriogram demonstrated a highly vascular lesion of the left side of the posterior fossa. During the period between January 1956 and January 1958 three

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explorations of the posterior fossa with partial resection of cerebellar hemangioblastoma tissue and three percutaneous taps of cerebellar cysts were performed to relieve the symptoms of increased pressure in the posterior fossa. On pathologic examination the resected cerebellar tumor tissue showed numerous small channels lined by endothelial cells. The stroma between the channels had a reticular appearance containing cells with large pale nuclei with granular cytoplasm as well as cells with small dark irregular or oval nuclei. No mitotic figures or blood pigment was present.

The patient was admitted to the Metabolism Service of the National Cancer Institute on March 18, 1958, for hematological studies, three months following his most recent operation. Physical examination revealed a thin, well developed active man. His blood pressure was 105/75 mm. Hg, pulse rate 80, respiratory rate 20. The patient did not have cyanosis and showed no evidence of clubbing or edema. Examination of the eyes revealed a right inferior nasal field defect. The pupils were equal and reacted normally to light. There was a large mid-vitreous opacity in the right eye and marked tortuosity of the retinal veins. There were no cardiac or pulmonary abnormalities. There was no splenomegaly. There were no abnormalities of the cranial nerves other than the quadrantic field defect already mentioned and bilateral nystagmus on lateral gaze. Motor power and sensation were intact throughout. The deep tendon reflexes were equal and active. The patient showed difficulty with rapid alternating movements and demonstrated past pointing, ataxia and intention tremor bilaterally but most marked on the left. The patient walked on a wide base with a tendency to fall to the left.

Laboratory examination on this admission revealed the following: a hematocrit of 58 per cent; hemoglobin 17.3 gm. per cent; red blood cell count 6.1 million per cu. mm.; white blood cell count 7,500 with a normal differential; platelet count 254,000 per cu. mm.; and reticulocyte count 0.9 per cent. No significant quantity of methemoglobin or sulfhemoglobin was present. The arterial oxygen saturation was 95 per cent. The bone marrow showed erythroid hyperplasia with a myeloid:erythroid ratio of 2 to 1. Results of urinalysis were completely normal. Cytologic examination of the urine for neoplastic cells was negative. The blood urea nitrogen, blood glucose, cholesterol, protein bound iodine, electrophoretic pattern and results of liver function studies were all normal. The electrocardiogram and the electroencephalogram were within normal limits.

The roentgenogram of the chest and fluoroscopy showed no pulmonary or cardiac abnormalities. No renal pathology was seen on two intravenous pyelograms. Fluid aspirated from the cerebellar tumor contained 4 to 6.1 gm. per cent protein. The electrophoretic pattern of this fluid was comparable to that of the patient's serum.

SPECIAL STUDIES

Methods. The total red cell volume was measured by the dilution of autologous red cells labeled with 100 μc. of Cr^{51} as sodium chromate [*41*]. The excess of Cr^{51} was reduced with 50 mg. of ascorbic acid [*42*]. The plasma volume was calculated from the measured total red cell volume and the peripheral hematocrit. The apparent red cell survival $T\frac{1}{2}$ was estimated from the change in specific activity of Cr^{51} over the period one to thirty days after infusion. No correction was made for the elution of Cr^{51} from apparently intact red cells.

Plasma and red cell iron turnovers were measured by the single dynamic pool model of Huff et al. [*43*]. Autologous plasma was labeled with 12 μc. of Fe^{59} citrate for injection. The samples were counted in a well type scintillation counter with a single channel spectrometer to a counting error of 3 per cent. Correction was made for physical decay.

The body surface count rates over the liver, spleen and cerebellar tumor (then protruding through a craniotomy defect) due to Cr^{51} and over the spleen, liver, sacrum and tumor due to Fe^{59} were measured by the method of Elmlinger et al. [*44*].

The erythropoiesis stimulating activity of ventricular fluid, spinal fluid, concentrated urine, untreated and concentrated plasma, of normal subjects and of the patient were studied by the assay of the fasted rat for erythropoietin of Fried et al. [*45*]. Fluid aspirated from the cystic cerebellar tumor of the patient was also assayed by this technic: Groups of seven to ten female Sprague Dawley fasted rats weighing 140 to 160 gm. were utilized as the recipient animals. The material to be assayed was injected subcutaneously twenty-four and forty-eight hours after the onset of the fast. Citrate (0.5 μc. of Fe^{59}) was injected intraperitoneally at eighty hours. The rats were bled sixteen to eighteen hours following the administration of the isotope, and the hematocrit, reticulocyte count and incorporation of Fe^{59} into red blood cells determined, assuming a blood volume of 5 per cent of the body weight for all recipients. The deproteinized extracts of the plasma were made according to the method of Borsook et al. [*46*].

RESULTS

The results of the isotopic studies are shown in Table 1. The normal values are taken from the literature [*41,43*]. This patient had a significantly elevated total red cell volume of 44 cc. per kg. with a normal plasma volume. The apparent Cr^{51} red cell life span ($T\frac{1}{2}$) was twenty-six days, within the normal range. There was no significant radioactivity due to Cr^{51} on *in vivo* counting over the liver or spleen that would indicate accelerated red cell destruction.

TABLE I*

THE BLOOD VOLUME, IRON TURNOVER AND RED CELL LIFE SPAN IN NORMAL SUBJECTS AND IN A PATIENT WITH CEREBELLAR HEMANGIOBLASTOMA

Test	Results of Normal Subjects	Results in a Patient
Cr^{51} red blood cell volume (cc./kg.)	29 ± 2	44
Cr^{51} plasma volume (cc./kg.)	35 ± 3	39
Cr^{51} red blood cell $T\frac{1}{2}$ (days)	29 ± 3	26
Plasma Fe^{59} $T\frac{1}{2}$ (min.)	102 ± 12	69
Red blood cell Fe^{59} uptake (%)	80 ± 5	89
Plasma Fe turnover (mg./kg./day)	0.35 ± 0.04	0.49
Red cell Fe turnover (mg./kg./day)	0.26 ± 0.03	0.44

* Normal is 41,–43.

The rate of red cell synthesis was increased, as estimated from the plasma and red cell iron turnovers, to 0.49 and 0.44 mg. per kg., respectively. The increase in red cell iron turnover was proportional to the increase in the red cell mass.

The results of the body surface Fe^{59} scan are shown in Figure 1. There was a normal pattern with rapid uptake and release of Fe^{59} over the sacral marrow, indicating red cell synthesis. No significant uptake was noted over the tumor

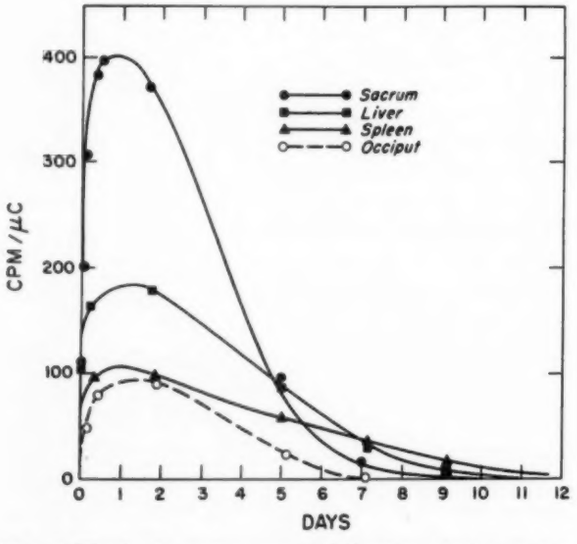


FIG. 1. The body surface counts following administration of Fe^{59}. The points represent the counts per microcurie of Fe^{59} injected over the organs corrected for the counts in the blood circulating in the organs.

TABLE II

ERYTHROPOIETIN ASSAY

Volume of Fluid (assayed per injection of the rat)	Red Blood Cells Fe^{59} Uptake at Sixteen to Eighteen Hours (%)	Reticulocytes per 1,000 Red Blood Cells
Two cc. of normal plasma	6.9 ± 1.3	2 ± 1
Three-fourths cc. of patient's tumor fluid	32.5 ± 4	41 ± 12
Two cc. of patient's plasma	6.6 ± 1.1	...
Deproteinized concentrate of 20 cc. patient's plasma	6.5 ± 1.4	...
Two cc. of normal spinal fluid	6.7 ± 1.3	...
Two cc. of patient's spinal fluid	6.8 ± 1.1	...
Concentrate of four hour excretion of normal urine	6.5 ± 1.5	...
Concentrate of four hour excretion of patient's urine	5.3 ± 1.7	...

which protruded through a craniotomy defect, or other extramedullary sites.

The results of the assay of erythropoiesis stimulating activity are shown in Table II. On subcutaneous injection of 0.75 cc. of the cerebellar tumor cyst fluid there was a marked stimulation of erythropoiesis in the fasted rat, as shown by an increased incorporation of Fe^{59} into the red cells and reticulocytosis compared to animals that received 2 cc. of normal plasma or spinal fluid. No erythropoiesis stimulating activity was found in the concentrated urine, plasma, ventricular or spinal fluid of the patient. It must be noted that the assay is sensitive to only marked increases in erythropoietin activity. No significant differences were noted in the mean hematocrits of the various groups studied, excluding the possibility that any of the agents administered were hemolytic. Four groups of six rats were given 25 mg. of testosterone, 25 mg. of hydrocortisone, 25 mg. of triiodothyronine or 40 units of ACTH per rat. The mean eighteen hour Fe^{59} red cell incorporation of each of these groups of rats was between 5 and 7 per cent of the radioiron administered, comparable to normal plasma or spinal fluid. This differentiates any of the known erythropoietically active substances related to the pituitary from the active substance in the cerebellar tumor fluid.

Preliminary studies have indicated that the erythropoietically active substance in the tumor fluid is stable on freezing and thawing, non-

dializable, and partially but not completely inactivated by boiling for five minutes.

COMMENTS

Since the reports of Carpenter, Schwartz and Walker [*25*] and Medvei [*8*], forty cases of polycythemia in association with cerebellar hemangioblastomas and forty cases of polycythemia in association with renal neoplasms have been reported. From 9 to 20 per cent of large series of patients with cerebellar hemangioblastomas have been found to have polycythemia [*28,30, 33,40*], whereas only 1 to 4 per cent of patients with renal tumors have polycythemia [*17,20–23*]. The mean age of the patients with cerebellar hemangioblastomas and polycythemia was thirty-seven years at first observation [*24–40*], while the mean age of onset of symptoms in patients with cerebellar hemangioblastoma alone in various series was from thirty-one to forty years [*47–49*]. The mean age of diagnosis of polycythemia in association with renal tumors and polycythemia vera is fifty-six [*8–23*] and fifty-two years [*50*], respectively. Eighty-two per cent of the patients with the association of polycythemia and cerebellar tumors are males [*24–40*] while 59 per cent of all patients with cerebellar hemangioblastomas are males [*48–49*]. The white cell count was normal in all but one of the twenty-five patients with polycythemia and cerebellar tumors for whom it was reported. The platelet count was increased in only one of nine cases. The spleen was not palpated in any instance. The bone marrow showed erythroid hyperplasia in seven cases [*31,35,37,39*] and was described as normal in two [*30,31*]. Two patients of this group were shown to have only relative polycythemia, that is a normal total red cell volume but a subnormal plasma volume [*40*]. In eight other cases a definite increase in the circulating red cell volume was observed [*25,36, 37,39,40*]. In all twenty-one patients in whom hematologic studies were performed after resection of the cerebellar hemangioblastoma the peripheral red cell indices returned to normal [*25–27,29,34,35,37,40*]. In six cases there was return of the polycythemia with regrowth of the tumor [*30,36,38,40*].

An interesting observation first emphasized by Lindau [*47*] is that the two tumors associated with polycythemia, i.e., hypernephroma and cerebellar hemangioblastoma, have been found in association in the same patient in at least nineteen cases [*47,51–60*]. In addition, the cells of the cerebellar hemangioblastoma have been described as similar to those of the hypernephroma [*34,48*]. In patients with Von Hippel-Lindau's syndrome, such as the patient described herein, one may see retinal hemangiomas and cysts of the pancreas and kidneys as well as the renal, adrenal and cerebellar tumors [*47*]. Lindau [*47*] suggested that the widespread abnormalities of this syndrome represent a generalized mesoblastic abnormality originating during early fetal development.

Many theories have been proposed to explain the association of polycythemia and cerebellar tumors. Ward, Foltz and Knopp [*37*] considered the possibility that this might be only a chance association of the tumor with polycythemia vera. The absence of splenomegaly or an elevation of the white cell or platelet count as well as the reversal of the polycythemia on resection of the tumor would appear to exclude this consideration.

Cramer and Kimsey [*30*] and Lebkowski [*34*] suggested that this very vascular tumor might be a significant site of erythropoiesis. Red cell production was not seen on pathologic section of the tumor in the present case or in the studies by Cushing and Bailey [*48*] or Meredith and Hennigar [*33*]. No incorporation and release of radioiron^{59}, as occurs in tissues that are actively producing red cells, was noted on *in vivo* scanning over the tumor in our patient.

Arterial anoxia due to medullary depression from pressure by the tumor has been seriously considered by Holmes, Kredel and Hanna [*31*] as the cause of the polycythemia. Two of the patients with cerebellar hemangioblastomas and polycythemia studied had oxygen saturations of 84 to 90 per cent [*37,39*], three others, including the patient presented herein, had oxygen saturations of 90 to 96 per cent [*31*]. That medullary pressure is not the major cause of the polycythemia is suggested by the fact that cerebellar hemangioblastomas constituted only 6 per cent of the cystic cerebellar tumors in the series of Cushing and Bailey [*48*] but are the only cerebellar tumors associated with polycythemia.

On the basis of our present studies the best hypothesis to explain the association of cerebellar hemangioblastomas and polycythemia is that the tumor produces a substance that stimulates the production of red cells by the marrow. The concept of a humoral stimulating factor as the fundamental stimulus for red cell production was first proposed by Carnot and Deflandre in

1906 [*61*]. Recent studies from various laboratories have confirmed the presence of such a hormone, erythropoietine, in the plasma and urine of anoxic, anemic and cobalt-treated animals [*62–64*]. The work of Jacobson et al. [*65*] and others [*66–68*] has suggested that the kidney is the major or even sole site of erythropoietin production and that the polycythemia in association with hypernephromas may be due to production of erythropoietine by the tumor cells or by obstruction of the renal vessels. The present study indicates that an erythropoiesis stimulating factor can be produced outside of the kidney, at least in pathologic states. No conclusions can be drawn concerning the chemical relationship of erythropoietin formed in response to anoxia and anemia and the active substance from the cerebellar hemangioblastoma, as neither substance has been fully characterized.

The production of an erythropoiesis stimulating factor by a cerebellar tumor suggests the possibility that the normal cerebellum, area postrema or other posterior fossa tissue might play a role in the control of red cell production.

SUMMARY

A patient with associated cerebellar hemangioblastoma and polycythemia is presented.

The circulating red cell volume was increased to 44 cc. per kg., the plasma volume was within normal limits. The apparent Cr^{51} red cell life span ($T\frac{1}{2}$) was twenty-six days. The plasma iron turnover and red cell iron turnover were accelerated to 0.47 and 0.44 mg. per kg. per day, respectively, indicating increased red cell synthesis. There was normal incorporation and release of Fe^{59} over the sacral marrow on body surface counting indicating red cell synthesis, but no production of red cells by the cerebellar tumor or other extramedullary sites.

Fluid aspirated from the cystic cerebellar tumor of this patient was shown to contain erythropoiesis stimulating activity when compared to normal plasma or spinal fluid. No significant increase of erythropoiesis stimulating activity was detected in the urine, plasma or spinal fluid of the patient. The active substance in the tumor fluid appears to be a non-dialyzable, partially heat-denaturable substance.

It is suggested that the polycythemia occurring in association with cerebellar hemangioblastomas is caused by increased production of red blood cells by the marrow in response to an erythropoiesis stimulating factor produced by the tumor.

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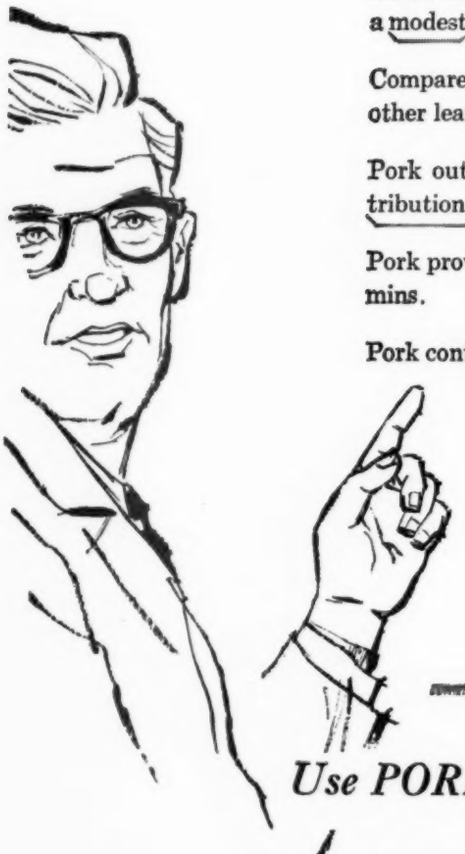
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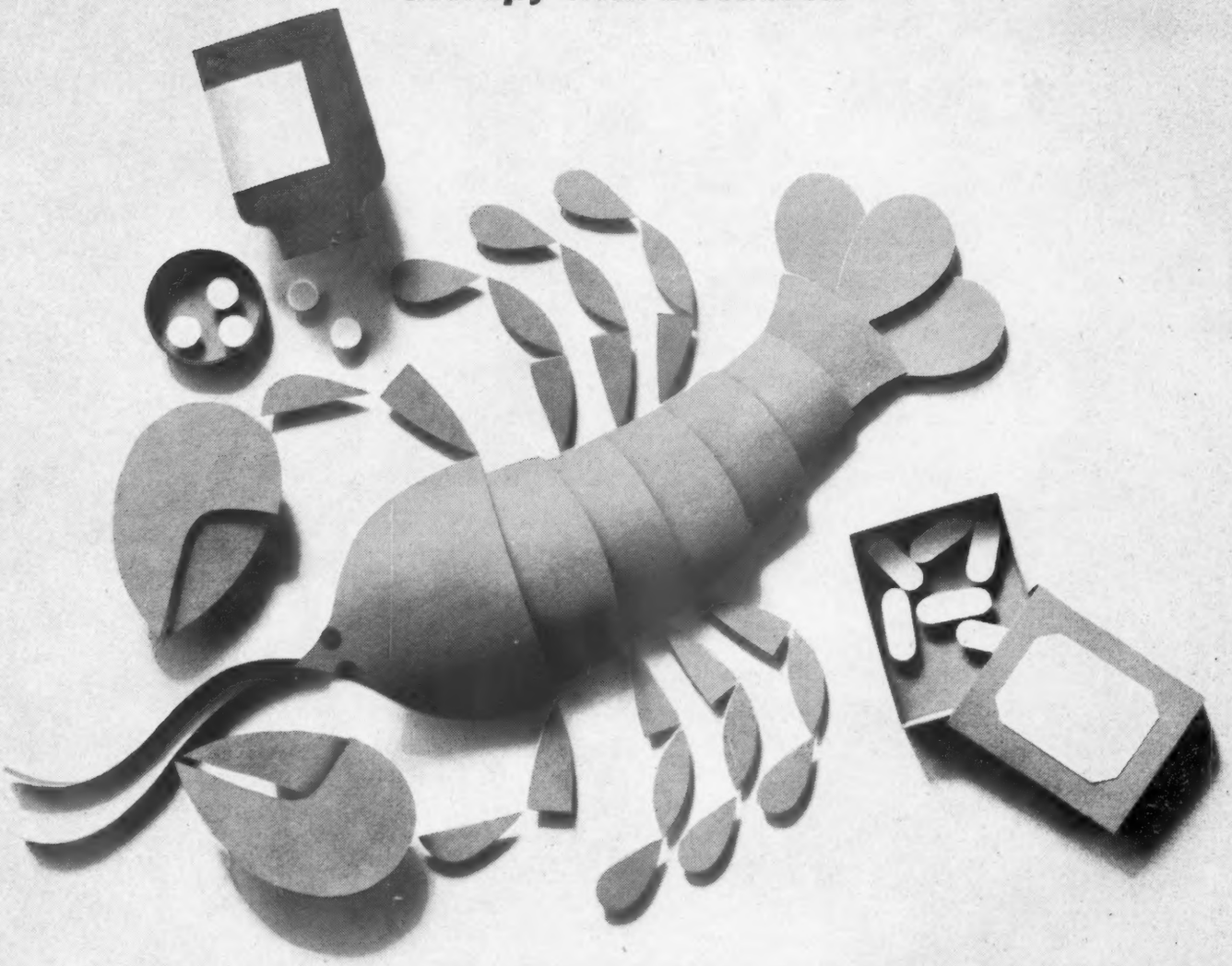
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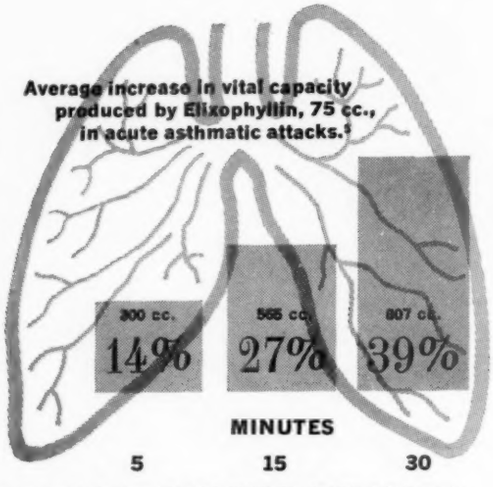
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in problem drinkers		allays anxiety—makes patient more manageable[3]	produces no significant depression of blood pressure, pulse rate, or respiration. No liver involvement reported
in preoperative tension and anxiety		allays anxiety without depression of vital functions[4]	reduces incidence of narcotic-induced respiratory depression and hypotension, relaxes skeletal muscle, smooths recovery and helps control emesis[4]
in pediatrics		allays tension in agitated, hyperkinetic patients	avoids danger of liver damage or other untoward reactions

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Vistaril acts rapidly in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear—whether occurring alone or complicating a physical illness. Used preoperatively and prepartum, Vistaril controls anxiety and fear, permits a substantial reduction in the amount of meperidine or other narcotic required for satisfactory analgesia, and helps prevent emesis. Vistaril's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with Vistaril, and it has a remarkable record of freedom from reactions.

INDICATIONS: Vistaril is clinically effective in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

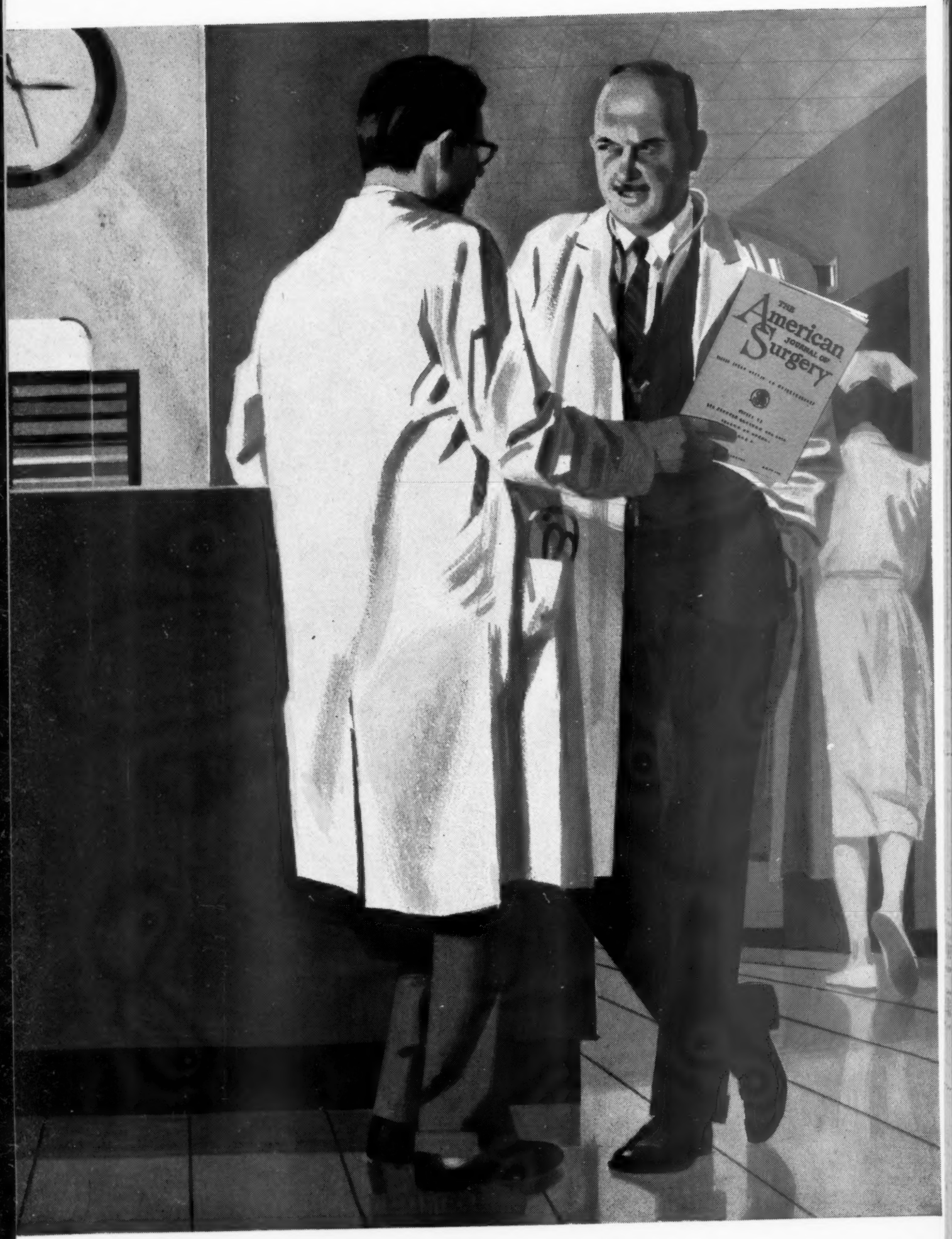
ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. *Recommended oral dosage:* In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially—adjust according to response. In cardiac arrhythmias: initial—25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic—50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. *Recommended parenteral dosage:* In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Capsules* (hydroxyzine pamoate)—25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate)—25 mg. per 5 cc. teaspoonful. VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride)—10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

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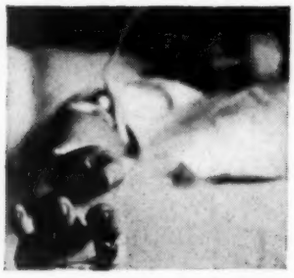
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Albamycin*

Indications — Albamycin is indicated in the treatment of staphylococcic infections, particularly in patients sensitive to other antibiotics or in the infections in which the organism is resistant to other antibiotics and sensitive to Albamycin, and in urinary tract infections due to microorganisms resistant to other commonly employed antibacterial agents but sensitive to Albamycin — notably certain strains of Proteus.

Administration and Dosage — Capsules and Syrup: The recommended dosage in adults is 500 mg. every twelve hours or 250 mg. every six hours, continued for at least forty-eight hours after the temperature has returned to normal and all evidence of infection has disappeared. In severe or unusually resistant infections, 0.5 Gm. every six hours or 1 Gm. every twelve hours may be employed. The dose for children is 15 mg. per kilogram of body weight per day for moderately acute infections; this may be increased to 30 to 45 mg. per kilogram of body weight per day for severe infections. These doses may be administered on schedules similar to those for adults.

Parenteral: Intramuscularly—5 cc. of Albamycin solution may be used directly by slow injection deep into the gluteal muscle.

Intravenously — it is recommended that 5 cc. of Albamycin solution be diluted further with 250 to 1000 cc. of sterile injection solution of sodium chloride, Darrow's solution, or Ringer's solution and administered by intravenous infusion, or by diluting to a suitable quantity and administered by continuous drip infusion. **Do not use with dextrose solution.** When it is necessary to use a smaller volume intravenously, 5 cc. of Albamycin solution may be diluted to a minimum of 30 cc. with one of the above diluents and administered slowly over a period of five to ten minutes to avoid irritation of the vascular endothelium. The dosage for adults is 500 mg. Albamycin administered either intramuscularly or intravenously every twelve hours. For children with moderately acute infections, the dosage is 15 mg. per kilogram of body weight per day. The daily dosage should be administered in two divided doses at intervals of twelve hours. As soon as the patient's condition permits, parenteral Albamycin should be replaced with oral Albamycin therapy.

Side Effects — Albamycin is a substance of low toxicity but is capable of inducing urticaria and maculopapular dermatitis. Leukopenia, which was rapidly reversible, has been reported in approximately 1% of cases. All of these side effects disappear rapidly upon discontinuance of the drug. In a certain few patients, a yellow pigment has been found in the plasma. This pigment is a metabolic by-product of the drug which, however, may interfere with determination of bilirubin and icteric index. Its presence is not associated with abnormal liver function tests or liver enlargement.

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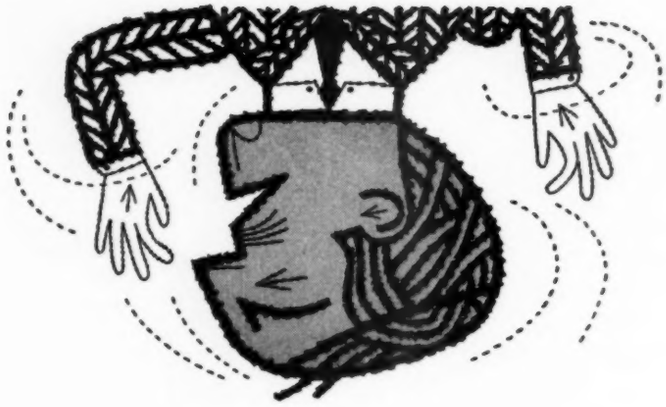
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vertigo is reversible



Antivert stops vertigo

moderate to complete relief of symptoms in 9 out of 10 patients[1]

Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. As with all vasodilators, ANTIVERT is contraindicated in severe hypotension and hemorrhage.

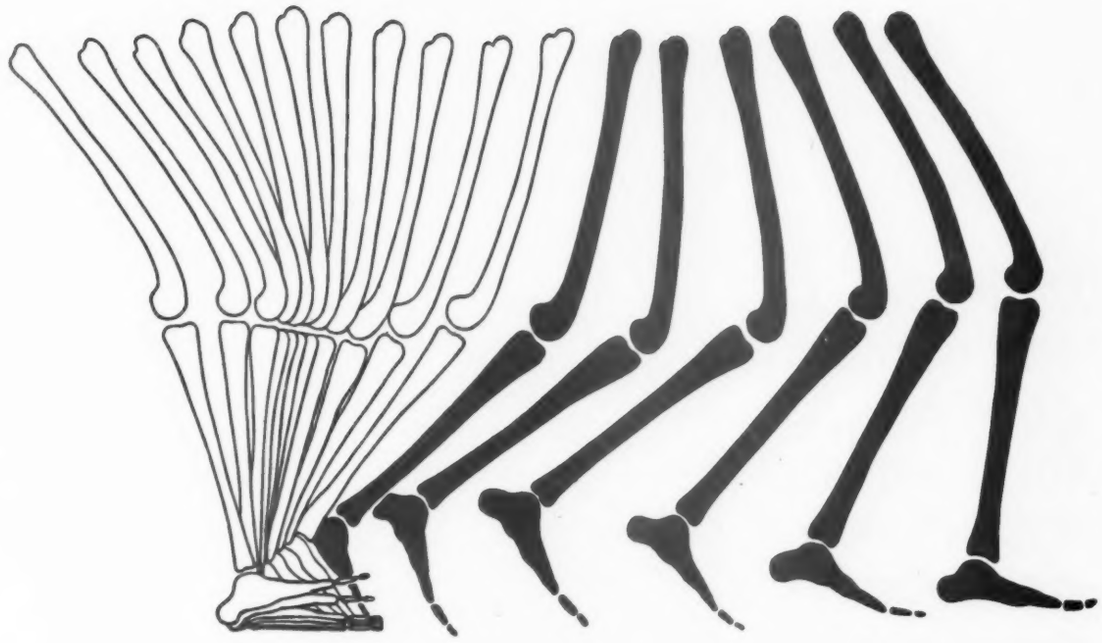
Supplied: Small blue-and-white scored tablets (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.) in bottles of 100. Syrup (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.) in pint bottles. Prescription only. Bibliography available on request.

Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

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Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.[1] "Post-injection flare-up was practically non-existent."[1]

relief within hours... lasting for weeks

Depo-Medrol* intra-articularly

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off. methylprednisolone acetate, Upjohn

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Patient M.J. ... one of the growing thousands of hypertensive patients controlled by Ismelin®

Mr. M.J., now 61, was admitted to a large teaching hospital in 1957 with mild pulmonary edema and severe hypertension (300/170 mm. Hg). Digitalis was given, along with reserpine and a ganglionic blocker.* He was discharged 16 days later, with blood pressure of 130/70 mm. Hg standing and 170/110 supine. Blood pressure, within 4 weeks, was 170/105 mm. Hg (sitting and standing). But ganglion-blocker therapy (alone or combined with chlorothiazide and/or rauwolfia) failed to hold blood pressure down and the side effects —syncope, lightheadedness, difficulty in evacuation and micturition— became increasingly troublesome.

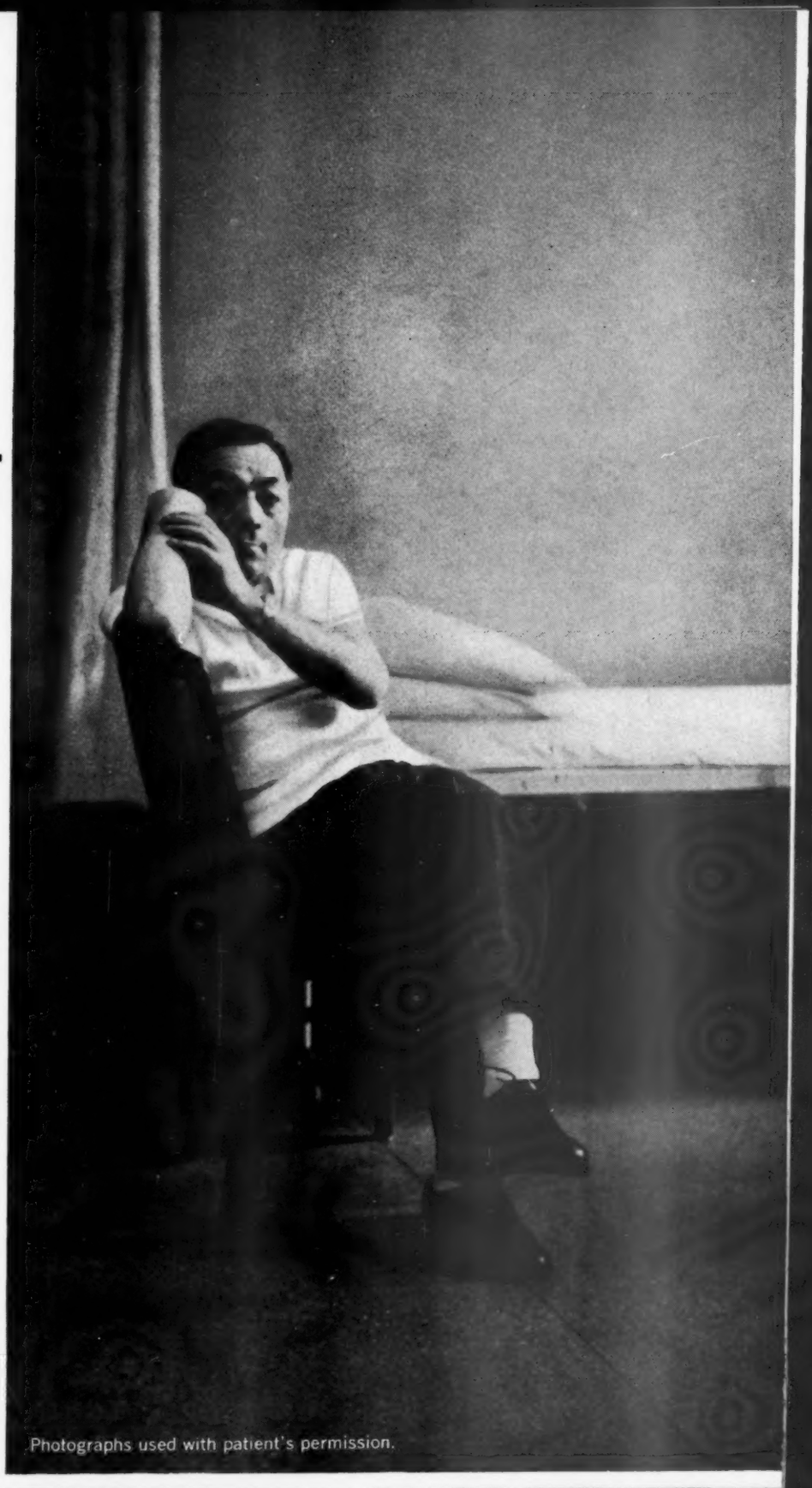
Blood pressure controlled with Ismelin— patient active and comfortable

On March 1, 1960, the ganglionic blocker was replaced with SU-5864 (Ismelin†). Within 5 weeks, Mr. J. was nearly normotensive and "felt 100% better."

As of October 5, 1960, blood pressure was 174/100 sitting and 130/80 standing. There was no evidence of tolerance to Ismelin.

*Therapy for this patient, during the 3½ years of treatment described here, included digitalis and one or more of the following: rauwolfia, thiazides, Serpasil-Apresoline.
†SU-5864 was introduced by CIBA as Ismelin® on July 5, 1960.

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Photographs used with patient's permission.





..."the most important new drug for the treatment of hypertension..."[1]

Following are representative comments from the ever-increasing published reports on Ismelin:

Patients on Ismelin have controlled blood pressures

"Only 1 of the 27 patients did not respond to treatment....The reduction of the systolic and diastolic pressures averaged 11/13 per cent in the supine position, 17/17 per cent in the sitting position, and 25/22 in the erect position. There were, of course, varying responses in the blood pressure from patient to patient, but generally blood pressure reduction was consistent in all three positions. The postural effect was most striking."[2]

"...Guanethidine [Ismelin] is a potent agent which lowers the diastolic pressure in many cases previously resistant to therapy with rauwolfia, hydralazine, hydrochlorothiazide, and ganglionic blockade."[3]

"Though our experience is limited, we have little doubt that guanethidine [Ismelin] is at present the drug of choice [for severe hypertension]. Its action is apparently steady; tolerance does not develop; and outpatient care of cases is relatively easy."[4]

"The use of this extremely potent drug led in all cases, which were treated both in hospital and on an ambulatory basis, to a clear-cut reduction in blood pressure, often even to normal levels."[5]

Hypertensive patients on Ismelin are relatively comfortable

Ismelin, because it is the selective sympathetic inhibitor, allows patients to be relatively comfortable. Ismelin suppresses sympathetic function with virtually no effect on the parasympathetic nervous system.

"In contrast [to the ganglionic blocking agents], guanethidine [Ismelin] is a purely sympatholytic agent with a hypotensive potency similar to that of the ganglion blocking compounds but with a lesser incidence of accompanying untoward effects."[6]

"The absence of tachycardia distinguishes the action of guanethidine [Ismelin] from that of adrenergic blocking drugs..."[2]

"Guanethidine [Ismelin], administered alone, was given to 40 hypertensive patients without serious side effects."[7]

"Notably absent were the constipation, paresis of visual accommodation, and dry mouth characteristic of the parasympatholytic effects of ganglion blocking drugs."[8]

"The absence of constipation was especially noteworthy."[9]

"Diarrhea has been mild and easily controlled."[10]

"Dry mouth, constipation, and difficulty in micturition were not encountered in this study. Those patients who had previously been on ganglion blocking therapy were relieved of these symptoms remarkably quickly, as well as of blurring of vision, when [Ismelin] was substituted."[11]

"No serious side effects were seen, and all could be alleviated or abolished by reducing the dosage."[7]

Physicians note that patients prefer Ismelin

"The majority of patients preferred guanethidine [Ismelin] over their previous antihypertensive medications; those previously treated with ganglionic blocking agents were particularly grateful for relief of constipation and visual difficulties."[7]

"We believe that use of it lessened anxiety in our patients. Most were better satisfied with guanethidine than they had been with previous ganglion blocker therapy."[11]

"Unlike the impotence experienced after ganglionic blocking agents, ability to obtain an erection was not impaired."[2]

"Guanethidine [Ismelin] has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy."[11]

"Most patients who had been treated previously with ganglion-blocking drugs expressed a strong preference for guanethidine."[12]

"Life need no longer be made a misery by the parasympathetic effects of the ganglion-blocking agents."[4]

For complete information about Ismelin (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N. J.

SUPPLIED: **Tablets,** 10 mg. (pale yellow, scored) and 25 mg. (white, scored); bottles of 100.

REFERENCES: 1. Kirkendall, W. M., Freis, E. D., and Moyer, J. H.: Summary of panel discussion, "New Drugs in the Treatment of Hypertension," presented at the 33rd Scientific Sessions of the American Heart Association, St. Louis, Mo., Oct. 21, 1960. 2. Frohlich, E. D., and Freis, E. D.: Paper presented at a Symposium on Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 3. Clark, G. M., Edmonson, J., and Lefkovits, A.: Ibid. 4. Evanson, J. M., and Sears, H. T. N.: Lancet 2:387 (Aug. 20) 1960. 5. Jaquerod, R., and Spühler, O.: Schweiz. med. Wchnschr. 90:113 (Jan. 30) 1960 (translation). 6. Brest, A. N., and Moyer, J. H.: Paper presented at a Symposium of Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 7. Eagan, J. T., and Orgain, E. S.: Ibid. 8. Richardson, D. W., and Wyso, E. M.: Virginia M. Month. 86:377 (July) 1959. 9. Ford, R. V., and Fallis, N.: Paper presented at a Symposium on Guanethidine (Ismelin®), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 10. Page, I. H., and Dustan, H. P.: J.A.M.A. 170:1265 (July 11) 1959. 11. Kirkendall, W. M., Fitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Ibid. 12. Dollery, C. T., Emslie-Smith, D., and Milne, M. D.: Lancet 2:381 (Aug. 20) 1960.

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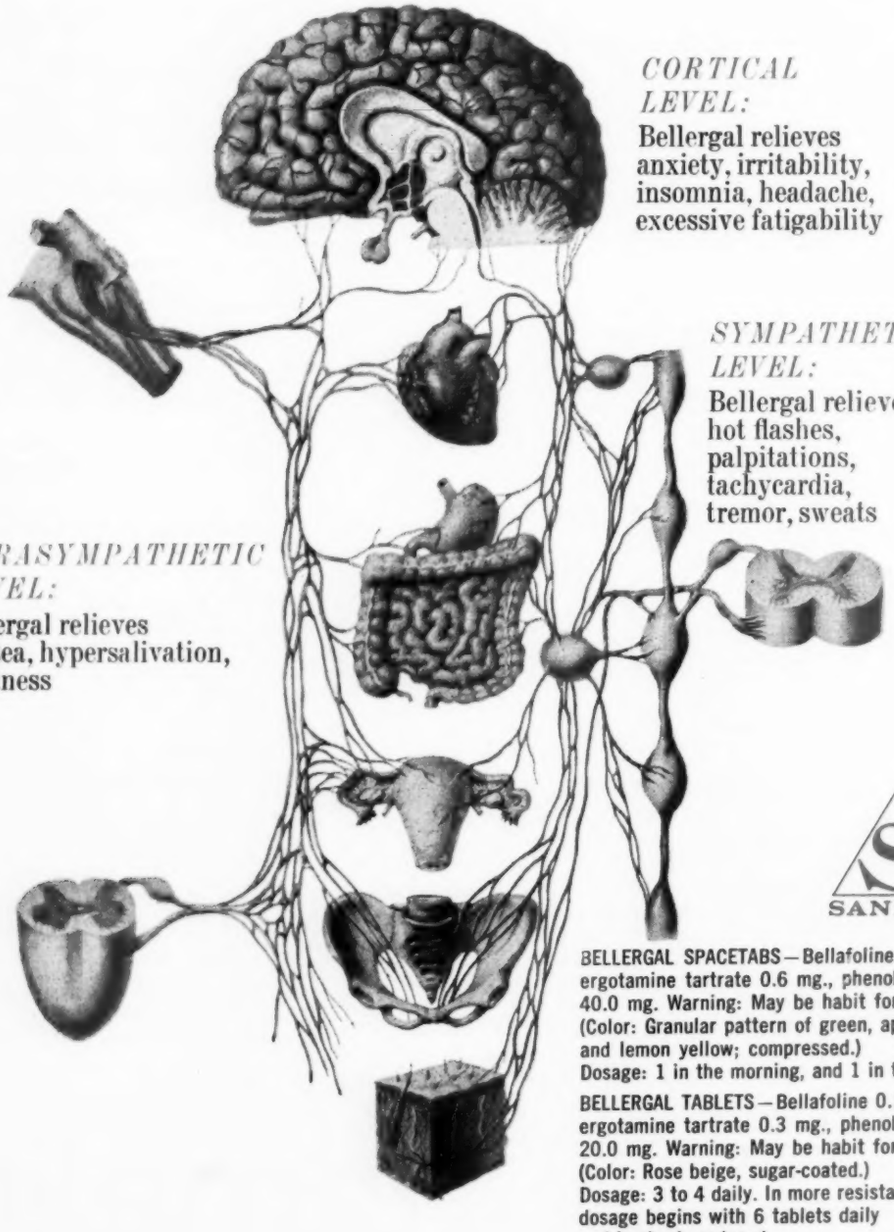
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BELLERGAL SPACETABS—Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.)
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Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.

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ANALGESIC: RELA "...diminished the need for administration of analgesic drugs [aspirin, codeine, meperidine]."[1]

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CLINICAL EFFECTIVENESS: "The effects of carisoprodol [RELA] were shown by relief of pain, and relief of localized muscle spasm..."[1]

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Bibliography: 1. Kestler, O. C.: *J.A.M.A.* *171*:2039 (April 30) 1960.

Complete information on RELA including indications, dosage, side effects, and precautions is available to physicians on request.

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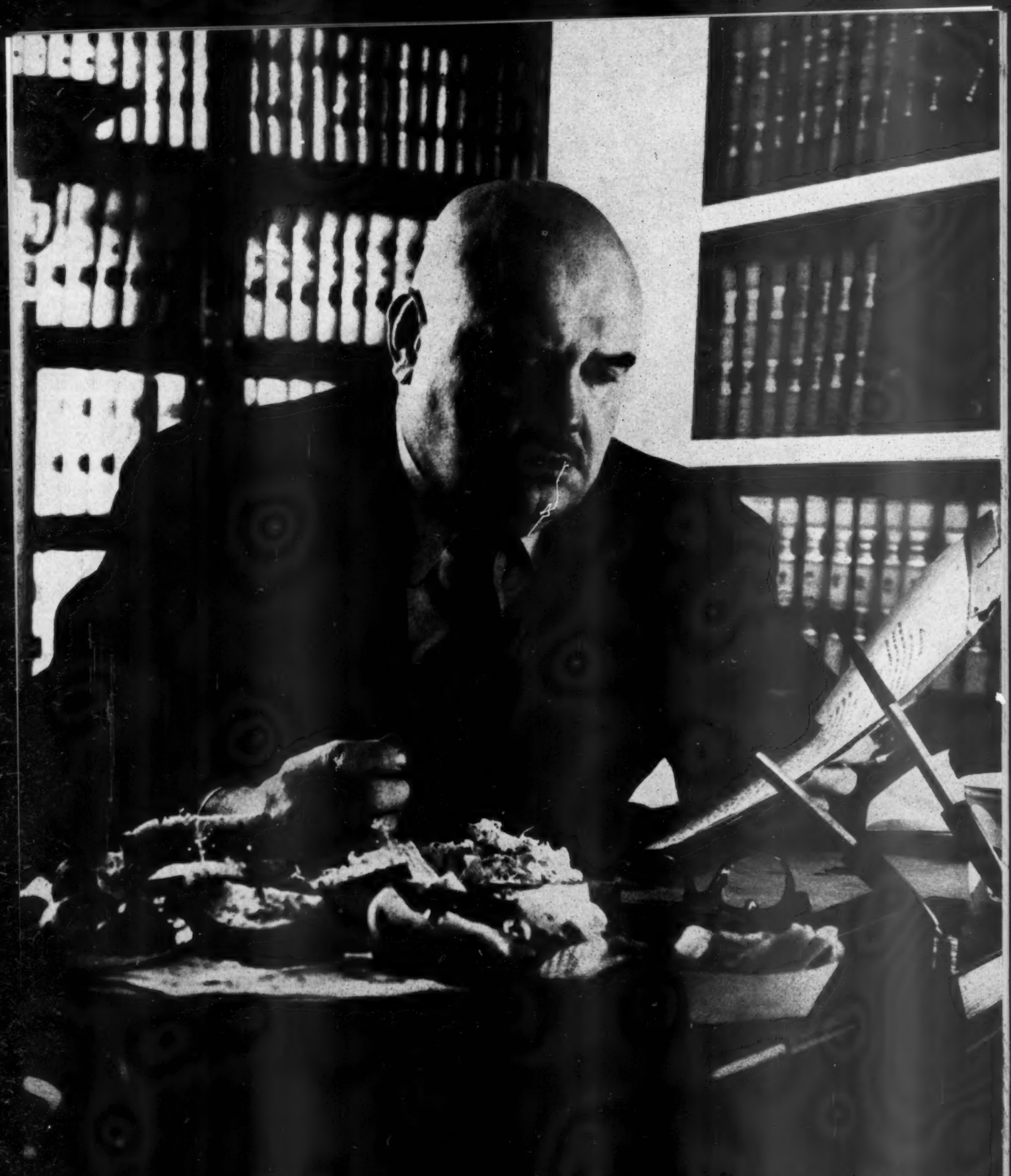
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provides remission of depression—smoothly, gradually, without "jarring" □ notably low incidence of serious complications or side effects □ convenience of once-a-day dosage

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In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinylhydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./*More detailed professional information available on request.*



for "special-problem" patients... when corticosteroid therapy is indicated

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in rheumatoid arthritis

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UNSURPASSED "GENERAL-PURPOSE" STEROID
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for example:

SPECIAL PROBLEM: ANXIETY-TENSION

When triamcinolone was used, euphoria and psychic unrest rarely occurred. (McGavack, T. H.: *Clin. Med.* 6:997 [June] 1959.)

SPECIAL PROBLEM: OVERWEIGHT

No patient developed voracious appetite on triamcinolone. Preferable for the overweight person whose appetite is undesirably stimulated by other steroids. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

SPECIAL PROBLEM: EDEMA

Since it does not produce edema, triamcinolone is useful in rheumatoid arthritis patients with cardiac decompensation who need steroid therapy. (Hollander, J. L.: *J.A.M.A.* 172:306 [Jan. 23] 1960.)

SPECIAL PROBLEM: HYPERTENSION

Triamcinolone may be included among the currently available antirheumatic steroids having the least tendency to cause sodium retention. (Ward, L. E.: *J.A.M.A.* 170:1318 [July 11] 1959.)

Hypertension did not result from triamcinolone therapy. Existing hypertension was reduced sometimes. This may have been due to lack of sodium retention. (Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L.: *Arthritis & Rheumatism* 1:215 [June] 1958.)

Precautions: Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. In the treatment of rheumatoid arthritis, dosage should be individualized and kept at the lowest level needed to control symptoms. Dosage should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

Supplied: Scored tablets—1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).
Also available—syrup, parenteral and various topical forms.

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Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.

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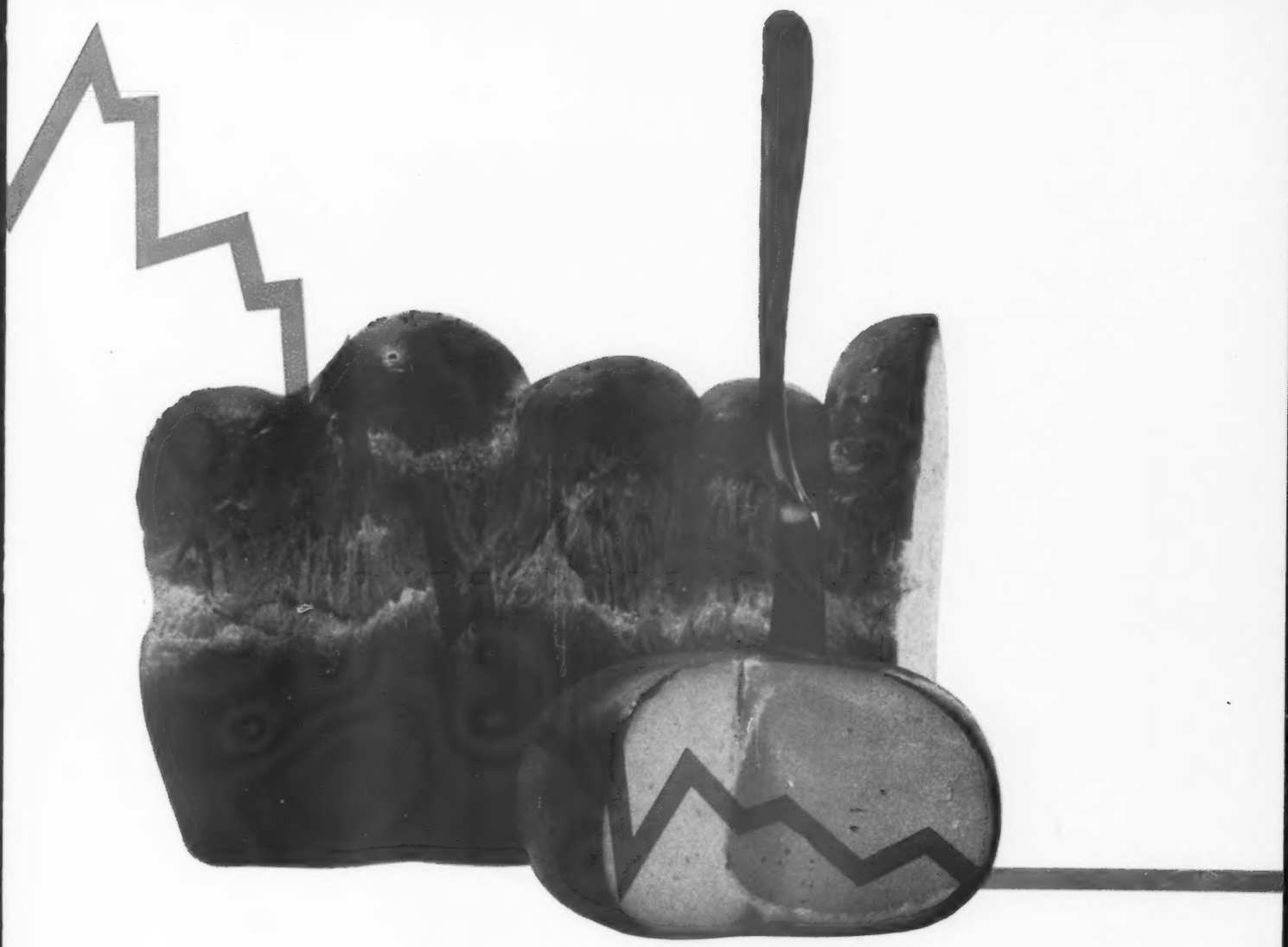
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Indications: Orinase is indicated as the therapeutic agent of choice in the majority of selected cases of adult or maturity-onset type of diabetes mellitus. In certain patients with labile diabetes, the use of Orinase as a supplement to insulin therapy may effect stabilization of the diabetic condition and lower insulin requirement.

Dosage:

Patients not receiving insulin — There is no fixed regimen for initiating Orinase therapy, but a suggested method is:

First day — 6 Orinase tablets (3.0 Gm.). **Second day** — 4 Orinase tablets (2.0 Gm.). **Third day** — 2 Orinase tablets (1.0 Gm.). **Fourth and subsequent days** — 2 Orinase tablets (1.0 Gm.) with increase or decrease as necessary to control glycosuria.

There is no fixed maintenance dose of Orinase; therapy may be individualized according to patient response. Adjust the maintenance dose (usually 1 to 4 tablets) to the smallest dose consistent with good control. The daily maintenance dose may be given once daily or in divided doses.

Patients receiving insulin (less than 20 units) — discontinue insulin and institute Orinase; (20 to 40 units) — initiate Orinase with a concurrent 30 to 50% reduction in insulin dose with a further careful reduction as response to Orinase is observed; (more than 40 units) — reduce insulin by 20% and initiate Orinase with a further careful reduction in insulin dosage as response to Orinase is observed.

Cautions: Observe all standard diabetes precautions: dietary restriction, weight control, exercise, hygiene, avoidance of infection, and adherence to dosage. As with exogenous insulin, changes in dosage may be necessary during the course of management. In the event of stress conditions, trauma or infection, increased dosage or supplementary animal insulin may be required.

Contraindications: Orinase as the sole therapeutic agent is contraindicated in juvenile diabetes; unstable or brittle diabetes; and diabetes complicated by ketosis, acidosis or coma.

Side effects: Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long term studies of hepatic function in humans and experience in over 600,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:

Tolbutamide ..... 0.5 Gm.

Supplied in bottles of 50.

References:

1. Bollinger, R. E., *et al.*: J. Kansas M. Soc. *61*:135 (March) 1960. 2. Williams, R. H.: Diabetes, New York, Paul B. Hoeber, Inc., 1960, pp. 491, 492. 3. Bradley, R. F.: Ann. New York Acad. Sc. *82*:513 (Sept. 25) 1959. 4. Sherry, S., *et al.*: Ann. New York Acad. Sc. *71*:249 (July 10) 1957.

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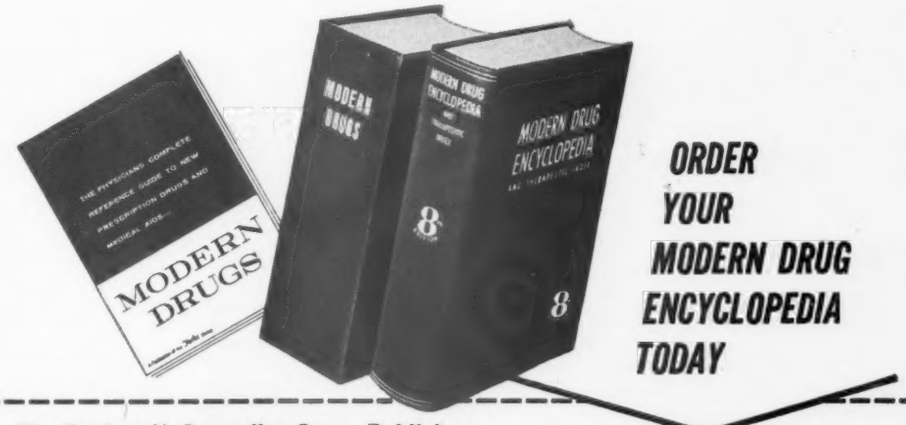
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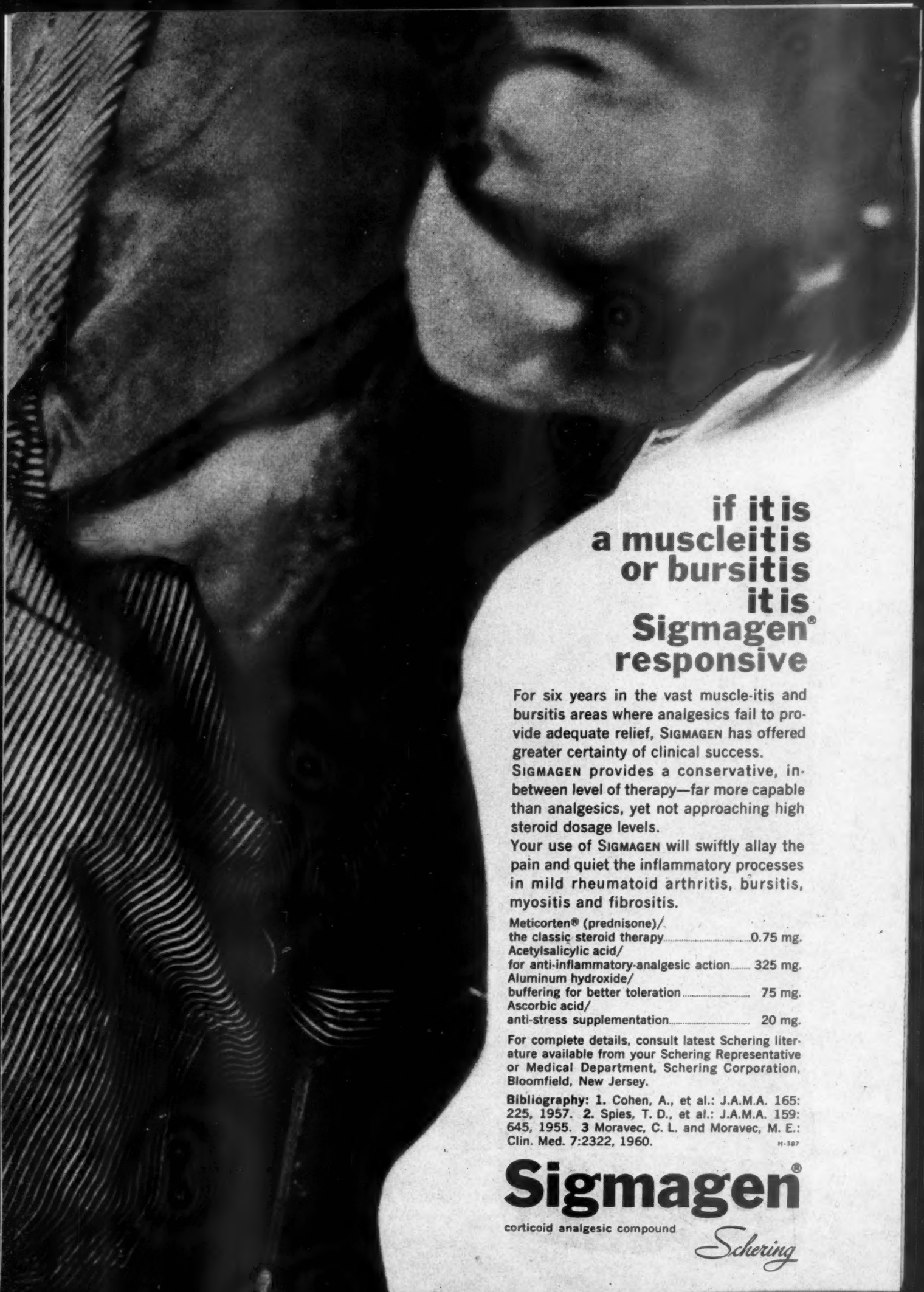
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Bibliography: 1. Cohen, A., et al.: J.A.M.A. 165: 225, 1957. **2.** Spies, T. D., et al.: J.A.M.A. 159: 645, 1955. **3** Moravec, C. L. and Moravec, M. E.: Clin. Med. 7:2322, 1960.

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1. A.M.A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, J. B. Lippincott Company, 1960, p. 363.
2. Friend, D. G., and Hamlin, J. T. III: in Modell, W.: Drugs of Choice 1960-1961, St. Louis, The C. V. Mosby Company, 1960, pp. 270-271.
3. Batterman, R. C., et al.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. 26:502-509 (Oct.) 1959.

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REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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*Natenshon, A. L.: Dis. Nerv. System *17*:392 (Dec.) 1956.

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